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The Impact of Anterior Cruciate Ligament Ruptures on Subchondral Bone Density in Collegiate Populations

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THE IMPACT OF ANTERIOR CRUCIATE LIGAMENT RUPTURES ON SUBCHONDRAL BONE DENSITY IN COLLEGIATE POPULATIONS

BY

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THESIS ACCEPTANCE PAGE

Zach Harbaugh

This thesis is approved as a creditable and independent investigation by a candidate for the master's degree and is acceptable for meeting the thesis requirements for this degree. Acceptance of this does not imply that the conclusions reached by the candidate are necessarily the conclusions of the major department.

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This thesis is dedicated to God, for His amazing love, sovereignty, and faithfulness. To my family, for their incredible support and encouragement throughout my educational journey. To my fiancée Danielle, for her constant love and dedication while I worked towards this advanced degree.

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ABBREVIATIONS

ACL	Anterior Cruciate Ligament
ADL	Activities of daily living
AE	Athlete exposure
cm	Centimeter
CVD	Cardiovascular disease
GRF	Ground reaction force
ISS	Injury surveillance system
kg	Kilogram
LE	Lower extremity
mg	Milligram
mRem	Roentgen equivalent man
MSI	Musculoskeletal injuries
NCAA	National Collegiate Athletic Association
OA	Osteoarthritis
pQCT	Peripheral quantitative computed tomography
PTOA	Post-traumatic osteoarthritis
ROI	Regions of interest
RTP	Return to play
USD	United States dollar
vBMD	Volumetric bone mineral density
VGRF	Vertical ground reaction force

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ABSTRACT

THE IMPACT OF ANTERIOR CRUCIATE LIGAMENT RUPTURES ON SUBCHONDRAL BONE DENSITY IN COLLEGIATE POPULATIONS

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The purpose of this study was to determine whether anterior cruciate ligament (ACL) rupture and reconstruction would lead to any significant changes in subchondral bone at the proximal tibia within 1 to 5 years post-surgical repair. Fifteen individuals (3 male, 12 female), aged 18 to 29 years old, who had sustained an ACL rupture and subsequent repair within the last 5 years were recruited for this study. An age and sex-matched control was recruited to match each participant. Subchondral volumetric bone mineral density (vBMD) of the proximal tibia was measured using peripheral quantitative computed tomography (pQCT). Additionally, jump force and efficiency were measured using a portable force plate as a means of determining muscle function. Total vBMD of the injured leg was greater in cases (276 ± 9 mg/cm^3) versus controls (231 ± 10 mg/cm^3) (P = 0.04). Total vBMD of the uninjured leg was not different between cases (256 ± 6 mg/cm^3) and controls (239 ± 6 mg/cm^3). All evaluated jump force and power values showed no significant difference between injured and uninjured legs in either the cases or the control group. Based on the results of this present study, we concluded that significant changes in subchondral bone could be seen within 1-5 years following ACL injury and reconstruction which may place injured individuals at a greater risk of developing post-traumatic osteoarthritis later in life. Future studies must be performed to determine the mechanism that is causing these changes in an effort to prevent problems later in life.

CHAPTER I

INTRODUCTION

While physical activity is one of the top preventative measures utilized to prevent or manage chronic conditions such as obesity, cardiovascular disease (CVD), and diabetes, maintaining a highly active lifestyle can increase an individual's exposure to chronic and acute musculoskeletal injuries (MSI).[1,2] It has been widely reported that sports participation, at any level, leads to higher incidence of MSIs compared to non-athletic activities.[3] However, one needs to consider that the risk of developing chronic conditions such as hip, knee, and ankle osteoarthritis may impact those who do not fall into a stereotypical classification of an "athlete". Populations who are at the greatest risk of suffering MSIs branch out beyond sport and recreation participants and includes those who participate in active service industries like the military and emergency first responders.[1,3,4] According to epidemiological studies, active individuals, including athletes, firefighters, and military service members are at 1.5 to 2.0 times greater risk of sustaining a MSI compared to their sedentary counterparts, making MSIs the leading cause of disability within active populations.[1,3-5] As a result, there has been a dramatic push by clinical providers to aggressively develop and implement preventative strategies to limit the risk of MSIs within active populations.

Subchondral bone, which lies directly beneath the articular cartilage of the knee is an area often affected by osteoarthritis (OA). A previous investigation using pQCT to measure subchondral bone revealed differences in the subchondral bone of individuals

with and without OA.[6] In this study, the participants did not have a history of ACL injuries and therefore were classified as having OA rather than PTOA. These findings are consistent with previous findings that spine areal bone density (aBMD) of the femoral neck and lumbar spine is greater in individuals with hip or knee arthroplasty resulting from OA and similar findings were reported in the offspring of these individuals.[7] Another study utilizing pQCT reported greater vBMD in the daughters and grandchildren of individuals with OA compared with controls.[8] These relationships may be partially explained by biomechanical modeling studies that have identified subchondral aBMD as a significant predictor of theoretical loads generated at the knee in children.[9]

Post-traumatic osteoarthritis continues to represent a major concern in the field of sports medicine; however, questions remain regarding the underlying processes that lead to the development of the condition. Our study aims to close this gap and investigate changes in subchondral bone following ACL repair and to determine if surgical technique and muscle function differences may have a role in these changes. We hypothesized that subchondral vBMD would be greater in participants with a history of ACL injury and that this difference would be isolated to the affected knee.

PURPOSE

The purpose of this study is to determine if subchondral bone changes occur within 1 to 5 years of an ACL injury and if these changes could place an individual at a greater risk of developing OA.

RESEARCH QUESTION

- In subjects who have sustained an ACL rupture, is subchondral bone density significantly greater when compared to controls 1 to 5 years following injury and if so, are they at a significantly higher risk of developing OA?

SPECIFIC AIMS

- To determine any significant changes in subchondral vBMD 1-5 years following ACL rupture in cases compared to controls.
- To determine the degree of muscle imbalances displayed between the involved and uninvolved legs after 1 to 5 years post-surgery.

HYPOTHESES

Hypothesis 1: We hypothesized that the affected leg of cases would have greater subchondral vBMD than the unaffected leg and also would have greater subchondral vBMD than the legs of controls.

Hypothesis 2: Cases will exhibit lower muscle function on their affected side than their unaffected side and controls.

ASSUMPTIONS

- All subjects will answer questions honestly and to the best of their ability
- All assessment tools have been appropriately maintained and calibrated daily
- All participants completed the muscle testing with maximal effort

LIMITATIONS

- Control subjects may have experienced previous knee trauma that has gone unreported
- There were small numbers of meniscus tears in case subjects
- The lack of available pre-injury data for either group
- Joint alignment was not measured in either control or case groups

CHAPTER II

REVIEW OF LITERATURE

Background and Epidemiology:

The greatest risk active individuals face is an injury to the lower extremity, the most common being hip, knee and ankle osteoarthritis, ankle sprains, chronic joint instability, and structural injuries to the knee.[1,2,4,10] Additionally these injuries can predispose an individual to sustaining a secondary injury.[4] Intrinsic risk factors such as a previous injury, age, a subject's level of neuromuscular control, and muscular strength can greatly predispose someone to injury.[11,12] These intrinsic risk factors can also impair neuromuscular control, which diminishes the dynamic muscular strength of the joints supporting musculature.[11,12] This eventually causes an active individual to begin a cycle of injury and re-injury due to the presence of intrinsic risk factors.[11] Army recruits who had sustained a previous ankle injury had a 13% increase in the incidence of an additional injury to the lower extremity.[4,13] Acute injuries are not the only concern when it comes to protecting athletes during regular bouts of athletic exposure. Current literature has fervently advocated for more research investigating the risk of chronic, non-contact injury.[10] The need for this additional research can be exemplified by a study conducted at the International Association of Athletics Federation World Athletic Championships. This study, comprised of 1486 athletes, was published in the Norwegian Journal of Sports Science and reported that overuse injuries comprise 44.1% of the injuries reported to research officials during the 2009 IAAF World Athletic Championships in Berlin,

Germany.[14] This was followed closely by acute non-contact injury's, accounting for another 13% of the injuries reported at the competition.[14]

At-Risk Populations:

Collegiate Athletes:

Collegiate athletes are one of the easiest populations in which implement an injury prevention tool. The National Colligate Athletic Association (NCAA) is aggressively looking to limit the number of injuries that occur while participating in collegiate athletics.[10] The NCAA Injury Surveillance System (ISS) was implemented in 1988 and recorded athlete exposures, and subsequent injuries, over the course of 16 years.[10,15] At its conclusion, the NCAA has cataloged over 1 million athlete exposures and collected reports of 182,000 injuries.[10,15] More than 50 percent of all injuries reported to the surveillance system involved the lower extremity (LE), with the ankle being the most common injury site, comprising 15% of all reported injuries.[10,15]

The ISS found that a total of 5,224,08 in-game athlete exposures lead to 72,316 subsequent in-game injuries, culminating in an in-game injury rate of 13.79/1000 Athlete Exposures (AE) over 16 years, across all divisions (DI – DIII) of college athletics.[10,15] Division I athletes experienced the highest in-game injury rate at 15.47/1000 AE, with division III athletes experiencing the lowest in-game incidence at 12.36/1000 AE. Interestingly enough, across all three NCAA athletic divisions, the number of practice exposures ranged from 4.5-5 times the number of in-game exposures yet this increase in exposures did not lead to and higher injury rate during practice compared to competition.[10,15] This difference in injury rate is most likely due to the difference in intensity between practice and in-game athletic performance. All these values account for all pre-season, in-

season and post-season exposures and injuries collected by the ISS. Game and practice injury rates differed significantly among all divisions ($P < 0.01$) and within each season ($P < 0.01$).[10,15]

Military:

While not normally included in the traditional athletic population, tactical athletes are a prime population to study injury exposure, risk, and incidence. Military strength and conditioning training is multidisciplinary and very closely mimics the high-risk training and competition that is performed by traditional athletic populations.[16] As with any training population, using techniques of progressive overload to increase strength, performance, and endurance is a delicate balance.[17] If this balance is skewed this overtraining can lead to the development of overuse and acute injuries.[17] Training exercises like loaded marches and contact drills in varying terrain are commonplace maneuvers used to increase soldier efficiency on the battlefield. According to the US Army Field Manual, depending on the exercise or the maneuver troops may be carrying anywhere from 21.7 to 68 kg of weapons, ammunition and gear.[18] Such drills and additional loads from body armor and packs can predispose recruits to sustain acute and overuse joint injuries and are commonly cited as a contributory factor in MSI development within the military, particularity the army.[19-21] Similar to civilian populations, additional risk factors from sustaining a MSI during military training include age, low levels of physical fitness, low levels of occupational and leisure-time physical activity before joining the military, history of previous MSI, smoking, biomechanical factors, flexibility, gender, and BMI.[13,19,21,22] A history of inactivity, prior injury and smoking all increase injury risk by weakening musculoskeletal structures in non-fit

individuals.[13,21,22] Strong associations have been established between lower levels of cardiovascular and musculoskeletal fitness and the increased incidence in overuse injuries, with Rosendal et al. showing the two to be inversely related ($P = 0.0001$).[23] These findings build on previous literature which stipulates that lower levels of fitness increase risk of MSI and that mechanical loading in untrained populations more often results in overuse injuries to deconditioned muscle tissue.[13,23-25]

With regards to injury rate among tactical athletes, it's expected that as many as 50% of recruits will suffer an injury during their basic military training.[26-28] A prospective cohort study found that when following 330 military conscripts through 8 to 12 weeks of basic training, an overall injury rate of 28% was established, resulting from an injury rate of 3.5 per 1000 soldier days.[23] Unsurprisingly, 65% of the injuries from that study were diagnosed as overuse, with 35% being diagnosed as acute.[23] A systematic review by Linenger et al. found that during basic military training, MSI rates ranged from 6 to 12 per 100 male recruits per month, increasing up to 30 per month within the Naval Special Warfare Training programs.[29] This review further calculated an incidence rate of 19.9 per 100 recruit-month for United States Marine recruits during basic training.[29]

In addition to the physical and emotional strain a MSI places on a soldier there is also the financial burden assumed but the United States government in addition to wages lost by the individual soldier. In the year 2000, it was estimated that the annual cost of training-related injuries within the US military was upwards of 100 million dollars.[5] In 2007, approximately 2.4 million medical visits to military treatment centers were related to MSI, totaling 548 million dollars in costs related to direct patient care.[30] A prospective cohort study in the U.S Army established that within their sample of 1,430 healthy

soldiers, over half of them (53.4%) sustained at least one MSI throughout a 12-month period resulting in 1.3 million dollars' worth of medical costs.[31] In 2016, it was estimated that at any moment, between 15 to 30% of the 1.3 million soldiers enlisted in the United States Armed Forces could be considered "medically not ready to deploy" due to MSIs, losing an estimated 6 billion dollars in salary.[32]

ACL Epidemiology:

While all MSI can have a significant impact on both tactical and traditional athletic populations, anterior cruciate ligament (ACL) ruptures are of particular interest due to their extreme impact on both short- and long-term joint health. ACL ruptures are an extremely common acute injury in sports. They result from sharp dynamic cutting movements which occur in sports such as football, basketball, and soccer. Approximately 100,000 ACL injuries occur in the United States each year with the number of ACL reconstruction performed in the United States ranging from 100,000 to 300,000 annual operations.[33-36] ACL injuries place a specific burden on the healthcare system, racking up an annual cost of approximately $625,000,000 USD in the United States.[34]

Civilian ACL Incidence:

Although evidence is currently limited, the incidence rate of ACL ruptures in the general population is estimated to be between 30 and 78 incidents per 100,000 people.[37-41] According to Sanders et al. and their 21-year population-based study out of the Mayo Clinic, the average age and sex-adjusted annual incidence of an isolated ACL tear was 68.6 per 100,000 person-years (95% CI, 65.4-71.8).[37] When adjusting for sex, the annual incidence of ACL injury in female subjects was highest between 14 to 18 years old, with an incidence of 227.6 per 100,000.[37] This incidence rate likely reflects female high-

school athletes.[37] When looking at female athletes competing in high-risk sports at the college level, incidence rates of 2.8 and 3.2 per 10,000 athlete exposures have been reported in women's collegiate basketball and soccer respectively.[42,43] Women are at 2 to 8 times as likely to sustain an ACL injury depending on the sport and level of competition, with college and high school female athletes suspected to suffer over 30,000 serious knee injuries every year.[44,45] However, ACL incidence does sharply decline in females age 19 to 25 likely resulting from the secession of competitive sports participation following high-school.[37] ACL incidence is most common in females during high school years but males experience the highest incidence overall during their college years and the years immediately following.[37] In males, the sex-specific annual incidence peaks between the ages of 19 and 25 years of age with 241.1 per 100,000 person-years, making this subcategory the highest incidence within any at-risk population according to Sanders et al. and their 21-year population study.[37]

Military ACL Incidence:

Tactical athletes are also at an increased risk of sustaining an ACL injury due to the physical demand of performing military duties. It's estimated that approximately 22% of all MSI occurring in the military setting occur at the knee, with 2,500 to 3,000 of these injuries being damage to the ACL.[31,46,47] ALC incidence in military populations has a huge impact on combat readiness of individuals soldiers and greatly impacts the quality of the overall fighting force.[48] While the ACL incidence rate of the general population is estimated to be 0.68 per 1,000 person-years, in a 5-year retrospective analysis of active duty service members, Owens et al. found that the homogenous high-demand military

population demonstrated an overall incidence rate of 2.96 per 1,000 person-years when controlling for both genders.[37,49]

ACL Risk Factors:

Research seems to point to altered lower body mechanics as the main culprit of ACL rupture, with 70% of ACL injuries resulting from a non-contact mechanism of injury.[35,50,51] Altered lower body mechanics are hypothesized to be a large contributor to these non-contact mechanisms and are likely a result of decreased neuromuscular control and/or a variety of anatomical risk factors.[42,52,53] MSI often lead to decreases in neuromuscular control, further establishing how having a history of MSIs greatly increases your risk of sustain another or more significant MSI.[54] A study looking at female athletes and the impact of neuromuscular control on posture and landing mechanics founds that participants who were currently injured had significantly different posture and landing biomechanical compared to uninjured participants.[54] Injured participants demonstrated increase knee abduction, increase intersegmental abduction moments, increased ground reaction forces and a shorter stance time during a 31cm drop jump landing task when compared to the uninjured group.[54] The correlation between decreased neuromuscular control and increased hip adduction and knee abduction is an important finding since knee abduction leads to the common "plant and twist" MOI for ACL rupture and is related to increased risk of ACL injury, re-injury or knee osteoarthritis.[52,53]

In addition to decreases in neuromuscular control, a variety of anatomic risk factors have been hypothesized to increase the risk of ACL ruptures.[42] Knee geometry is hypothesized to be a large predisposing risk factor to ACL injury, with increased

quadriceps angle (Q-angel), decreased width of the femoral notch via notch stenosis, and the depth and slope of the tibial plateau and menisci all suspected to largely impact the incidence of ACL injury.[42,55-57] Other anatomical risk factors can include the ACL's volume within the intercondylar fossa, anteroposterior knee laxity, generalized joint laxity due to capsular or rotary instability, subject BMI, and static malalignment of the lower extremity in cases of genu valgum, varum, and recurvatum.[42,51,58-60]

Anatomic and neuromuscular differences fall under the category of an intrinsic risk factor.[42,61] Additional, intrinsic risk factors to ACL rupture include previously described sex differences, hormonal risk factors, and genetic risk factors.[61] Genetics are an important intrinsic risk factor. ACL – injured individuals are 4-times as likely to have a close family member who has sustained a ligamentous injury compared to control populations.[62,63] Genetic risk factors can also present themselves at the DNA level, as some research is showing the those who sustain an ACL-injury experience the underrepresentation of the CoL1A1 genotype, a gene that encodes a protein chain primarily responsible for reinforcing type 1 collagen and other important structural components within the ligamentous tissue.[62,63] Cognitive risk factors like decreased reaction time, processing speed, visual and verbal memory have all been hypothesized as intrinsic risk factors that could lead to an increased risk of ACL rupture.[52,64] Additionally, cognitive risk factors are negativly impacted by fatigue, which could exacerbate their impact on athletes as they tire throughout a competition or practice.

Probably the most well researched and recognized intrinsic risk factors to sustaining any MSI, particularly ACL, is a history of a previous MSI.[62] Sustaining a previous ACL injury greatly increases your risk of re-rupture.[65,66] Data collected by the

NCAA during a 10-year injury surveillance study spanning 2004 to 2014 reported that in collegiate athletes, 1 in 9 ACL ruptures were recurrent, with 14% of recurrent ACL ruptures happening in females.[67] Ten percent of recurrent ACL ruptures occurred in males.[67] Kramer et al. also found that women who had sustained a previous ipsilateral ankle injury were also at a greater risk of sustaining an ACL injury ($P = 0.02$).[60]

Many of these anatomical, intrinsic risk factors have been theorized to contribute to the increased ACL injuries experienced by females, since females have smaller ACL's, a greater Q-angel, and greater knee laxity compared to males.[60,62,68,69] A rather controversial topic in the current literature is whether various hormonal risk factors play a role in the increased risk of MSI and ACL rupture. The current research has suggested that women are at an increased chance of ACL injury during the follicular (pre-ovulatory) and ovulatory phases of the menstrual cycle.[45,70] While this evidence is strongly supported within the literature more research needs to be done to further validate this research. Validating menstruation status continues to be the true limiting factor within study designs looking to determine how the menstrual cycle and hormonal changes impact a women's risk of MSI and ACL injury.[45]

Military Specific ACL Risk Factors:

Just like civilian populations, soldiers are at risk of sustaining an injury to the ACL when factoring in their abnormal knee geometry, previous history of ACL reconstruction, poor landing mechanics or reaction time, menstrual phase, BMI, generalized joint laxity or variations in collagen gene expression.[42,62] Risk factors specific to the military include lack of activity before joining the military and load-carrying during training.[21] Multiple studies have reported on how above-average BMI in

combination with a smaller intercondylar width index is associated with a significant increase in ACL rupture risk within military population.[62,71] Evans et al. found that above-average BMI and deceased intercondylar notch width significantly increase ACL risk ($P = 0.021$) when retrospectively reviewing 1,687 Naval Academy cadets.[71] These findings were substantiated by Uhorchak et al. who, after prospectively following 1,198 US Military Academy cadets over a 4-year period, reported that ligamentous laxity, a smaller intercondylar notch, and above-average BMI were all associated with a higher risk of ACL disruptions.[51] Like civilian populations, the vast majority of military ACL injuries are repaired to avoid further meniscus or chondral damage. However, even with this reconstruction, individuals who sustain an ACL rupture are still at great risk of incurring further joint damage via OA.

Post Traumatic Osteoarthritis:

The life-long impact of MSIs is most commonly an increase in comorbidities such as the early development of osteoarthritis, which can impact an individual's ability to carry out activities of daily living (ADLs) and leisure activities later in life.[2,12,72] Osteoarthritis (OA) is a chronic degenerative disorder commonly defined as the structural and functional degeneration of a joint, often leading to pain, stiffness and disability.[73-75] OA is the most common form of arthritis and impacts up to 15% of the population.[76] Over 27 million adults in the United States aged 25 years or older have been diagnosed with OA. This makes OA the most diagnosed disease in general medical practice.[75,77,78] OA prevalence is projected to double by the year 2020 due to the current size of aging populations and the staggering rate at which obesity is increasing.[78] OA is the leading cause of mobility-related disease in the United States.[78]

Specifically, at the knee, approximately 13 million adults in the United States, aged 60 years or older, have experienced the radiographic changes needed to be classified as radiographic OA.[75] Four million of those patients have been classified as having symptomatic OA.[75] Radiographic changes include the structural degeneration of the articular cartilage, resulting from the bone's decreased ability to absorb and dissipate forces. This lack of absorption capacity is due to an increase in trabecular bone density, the process in which spongy, force dissipating, trabecular bone is remodeled into hard, dense cortical bone. This bone remodeling can result in varying levels of disability and the onset of symptomatic OA.[73,74] Symptomatic OA describes OA that presents radiographically and/or symptomatically. Patient's with symptomatic OA will often experience pain, aching stiffness, and disability in the involved joint.[79-81] According to the National Health Interview Survey, approximately 14 million people in the United States have symptomatic knee OA.[82,83] The rampant development of hip and knee OA has catapulted the diseases into becoming the leading cause of lower extremity disability in elderly populations, with approximately 40% of all men and 47% of women at risk of developing the debilitating condition.[78]

While OA is commonly seen as a chronic disease experienced by elderly individuals, active individuals are actually at a very high risk of developing osteoarthritis as a secondary injury.[84] Secondary, or posttraumatic osteoarthritis (PTOA), can result from a multitude of etiologies ranging from metabolic, anatomical or inflammatory defects within the body.[79,84] These anatomical or inflammatory defects are almost always a result of a joint injury such as a fracture, cartilage damage, acute ligament rupture or chronic ligamentous instability.[75] Within active populations, significant joint trauma

poses one of the most common risks to developing secondary joint arthritis, especially if that injury results in the joint needing to be surgically reconstructed.[84,85] ACL ruptures, while traumatic by themselves, are often accompanied by additional damage to other anatomical structures within the knee such as damages to articular cartilage, subchondral bone, other fundamental knee ligaments, or menisci. Such collateral damage is observed in approximately 65-75% of all ACL knee injuries and is strongly suspected to be linked to the development of PTOA with a substantial percentage of patients showing changes in bone physiology and functional disability as early as ten years post-injury.[86,87] Current theories suggest that the injury-inducing force has caused significant tissue damage to the subchondral bone, thus initiating the degenerative process within the subchondral bone.[88] These changes in subchondral bone could increase the loads placed on articular cartilage leading to a greater risk of OA development. However, while the specific pathogenesis connecting ACL rupture and the onset of PTOA is not entirely known, current theories suggest that PTOA results from, or is accelerated by, higher BMI later in life, altered loading mechanics, decreased knee extension, or poor single-leg strength and proprioception of the involved limb one year after surgery.[77,89-92] Further, individuals with PTOA account for almost 12% of all symptomatic OA cases, making up 5.6 million cases of lower extremity OA in the United States.[93]

As of 2005, the treatment of PTOA has cost a total of 11.79 billion dollars with direct costs of the illness surpassing 3 billion dollars annually.[93] In the US, it is estimated that the average direct cost per-patient can vary from $1,442 to 21,335 dollars (adjusted to the 2015 equivalent).[94]

CHAPTER III

METHODS

Participants:

Participants for this matched case-control study were recruited primarily via word of mouth. Cases were recruited based on being 18 to 29 years old and having a history of an ACL injury in the past 5 years. In total, fifteen case participants (3 male, 12 female) were recruited for this study. Age and sex-matched controls were recruited and paired with each participant.

Questionnaires:

General health history questionnaires, in addition to orthopedic questionnaires, were administrated during the one-hour study visit (Appendix B). These questionnaires were used to determine whether a participant had any additional health factors that could have potentially affected subchondral bone. Additional factors were controlled for when investigating group differences.

Anthropometrics:

Participants' height without shoes was measured using a portable stadiometer manufactured by Seca (Seca, Chino, CA). Height was measured in centimeters and taken in duplicate, with measurements differing by more than 0.5 cm being repeated. Weight with light clothing was measured in kilograms and in duplicate, using a Seca, model 770, digital scale (Seca, Chino, CA). Height and weight measurements were rounded to the

nearest 0.5 cm for height and 0.1 kg for weight. Since height and weight are known predictors of bone outcomes, they were included in all statistical models.

Medical Records:

Each participant signed a release of medical records form for the individual facility that performed their surgery to obtain the relevant information regarding the type of procedure performed (Appendix D). The primary item of interest was the graft type used in each subject's surgical repair. Graft type has not been previously investigated as a risk factor for cartilage degradation. Additional information included the presence of secondary injuries such as meniscus tears.

Mechanography:

Ground reaction forces (GRF) and movement efficiency were measured using a Leonardo Mechanograph (NovoTec Medical, Carmel, CA). The first test consisted of the participant standing on the force plate and jumping as high as they could one time using both legs. The participant was not given any instructions other than to jump as high as they could and remain still after landing. This measure was repeated three times and the highest measurements from the three jumps were used for analysis. The next test involved a similar protocol. However, this time the participant performed a single-legged jump. This test was performed bilaterally, repeating the test three times on each leg. The results from these tests were used as a measure of muscle function and were used as an outcome variable to determine if muscle function and side-to-side leg differences were similar or dissimilar between participants with and without a history of ACL injury.

Subchondral vBMD:

Subchondral vBMD was measured by pQCT using a XCT 3000 (Stratec, Pforzheim, Germany). Scan settings included a voxel size of 0.5 mm and a scan speed of 30 mm/s. A scout scan of the tibiofemoral joint was performed; after which a reference line was placed on the proximal medial tibial plateau and an image was taken 2 mm distal to the reference line. Analysis settings were as follows: contour mode set to 2, peel mode set to 2, the trabecular bone threshold was set to 400 mg/cm^2 and the cortical bone threshold was set to 710 mg/cm^2.

Data Analysis:

Participant characteristics were compared between cases and controls using a student's t-test. Ordinary least squares regression was used to determine the effect of ACL injury on dependent variables while adjusting for covariates. Dependent variables included subchondral vBMD, jump force, relative jump power, and force efficiency. Additionally, the difference between the affected and unaffected legs was calculated for all outcome variables and these differences were used as dependent variables. Independent variables for vBMD models included group, time since surgery, and jump force. For models testing jump force, jump power, and force efficiency, time since surgery was tested as an independent variable. For all models, height and weight were controlled for as covariates. Data shown represent marginal mean ± SE. Data were analyzed using Stata version 13 (StataCorp. 2013. *Stata Statistical Software: Release 13*. College Station, TX: StataCorp LP).

CHAPTER IV

RESULTS

Participant Characteristics

Patient characteristics included age, height, weight, and BMI. These values were collected for in both case and control groups. After statistical analysis, no individual characteristic proved to be significantly different between the case and control group.

Table 1. Participant Characteristics by Cases and Controls

	Cases	**Controls**	**p-value**
*Age (Years)	20 [19-23]	20 [18-23]	0.936
Height (cm)	172.0 ± 6.0	172.5 ± 10.5	0.858
Weight (kg)	73.9 ± 15.5	72.2 ± 14.4	0.754
BMI (kg/m^2)	24.8 ± 3.8	24.1 ± 3.8	0.632

*Age is given as median [range]
Data are given as mean± SD

Volumetric Bone Mineral Density

Total vBMD of the injured leg was greater in cases (276 ± 9 mg/cm^3) versus controls (231 ± 10 mg/cm^3), ($P = 0.004$) (Figure 1). Total vBMD of the uninjured leg was not statistically different between cases (256 ± 6 mg/cm^3) and controls (239 ± 6 mg/cm^3), ($P = 0.07$) (Figure 1). A larger between-leg difference in vBMD was observed in cases compared to controls (28 ± 12 mg/cm^3 and 8 ± 9 mg/cm^3, respectively, $P = 0.04$) (Figure 2). Jump force, jump power, force efficiency, and time since surgery were all insignificant predictors of outcome variables in these models.

Jump Force, Power, and Efficiency

Double legged jump force, relative to body weight, showed no significant difference between case and control groups (Figure 3). Relative jump force percent difference showed no significant percentage difference between injured and uninjured legs in either the cases or the control group (Figure 4). Relative jump power, as well as relative jump power percent difference between legs, showed no statistical differences when comparing case and control groups (Figure 5, Figure 6). Force efficiency and the force efficiency percent difference between legs, also yielded no statistical differences when comparing case and control groups (Figure 7, Figure 8).

Additional statistical analysis showed that time since surgery was not a significant predictor of any outcomes. Neither jump force, power or efficiency predicted any differences or changes in subchondral bone. Fourteen out of fifteen subjects utilized an autograft for their reconstruction. The impact of graft-type on subchondral bone was unable to be investigated throughout this study.

Figure 1. Total vBMD of Injured and Uninjured Legs Between Cases and Controls

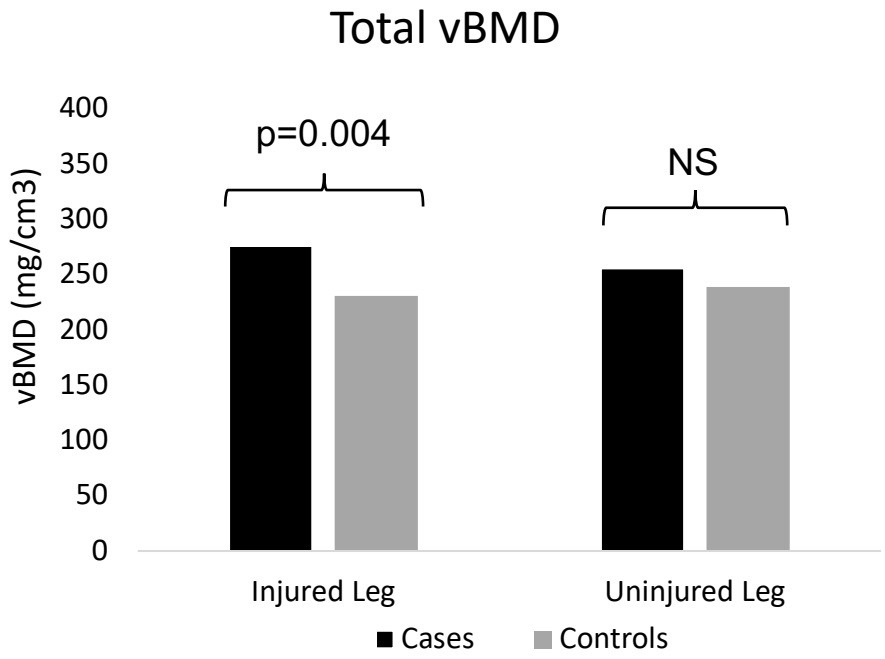

Figure 1. There was a significant difference in total volumetric bone mineral density between the injured legs of cases and the legs of controls.

Figure 2. Total vBMD Difference Between Injured Legs and Controls

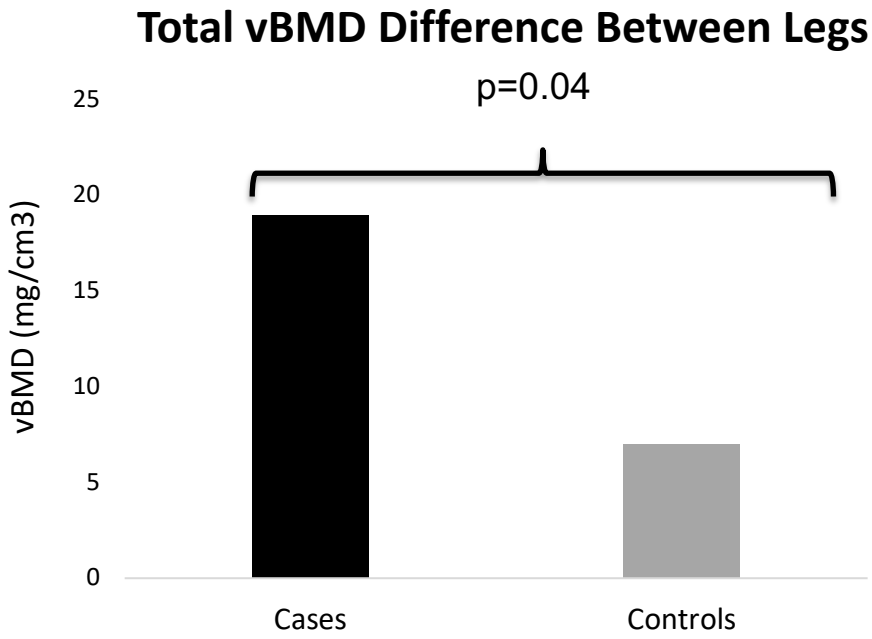

Figure 2. There was a significant difference between the difference in total volumetric bone mineral density between the injured and uninjured legs of the cases compared to the difference in total volumetric bone mineral density between the injured and uninjured legs of the controls.

Figure 3: Difference in Jump Force per Body Weight Between Cases and Controls

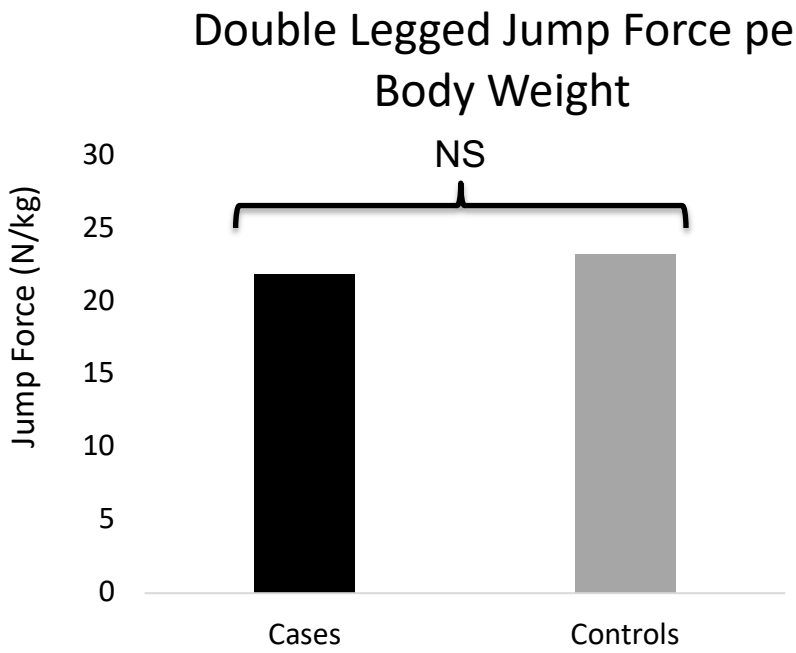

Figure 3: No significant differences were found when looking at the differences in double leg jump force per body weight compared between cases and control groups.

Figure 4: Difference in Relative Jump Force Percentage Between Legs

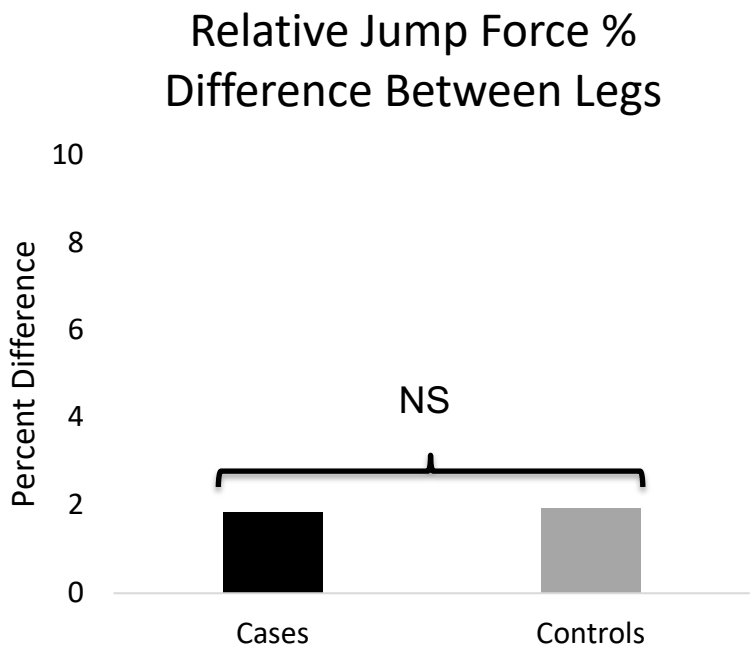

Figure 4: No significant differences were found when looking at the percentage difference in the relative jump force between legs and comparing these differences between cases and control groups.

Figure 5: Difference in Relative Jump Power Between Cases and Controls

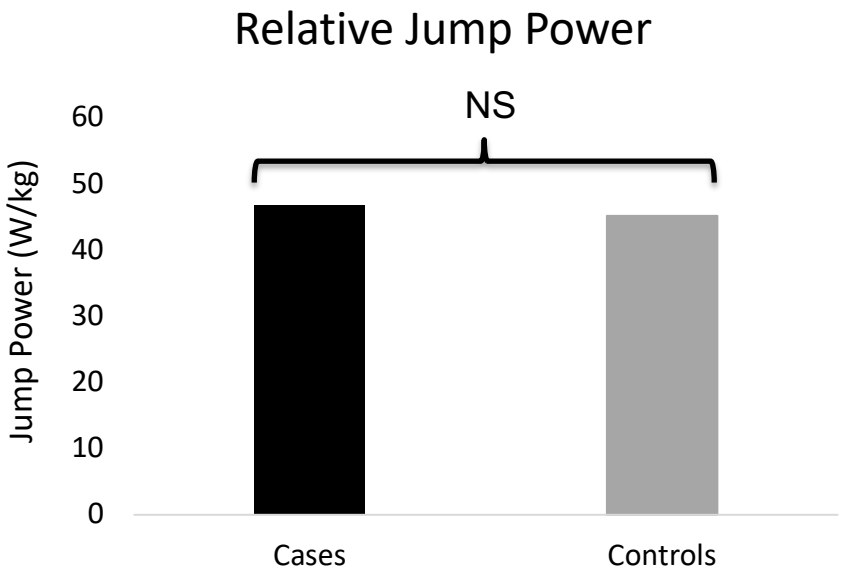

Figure 5: No significant differences were found when looking at the differences in relative jump power between cases and control groups.

Figure 6: Differences in Relative Jump Power Percentage Between Legs

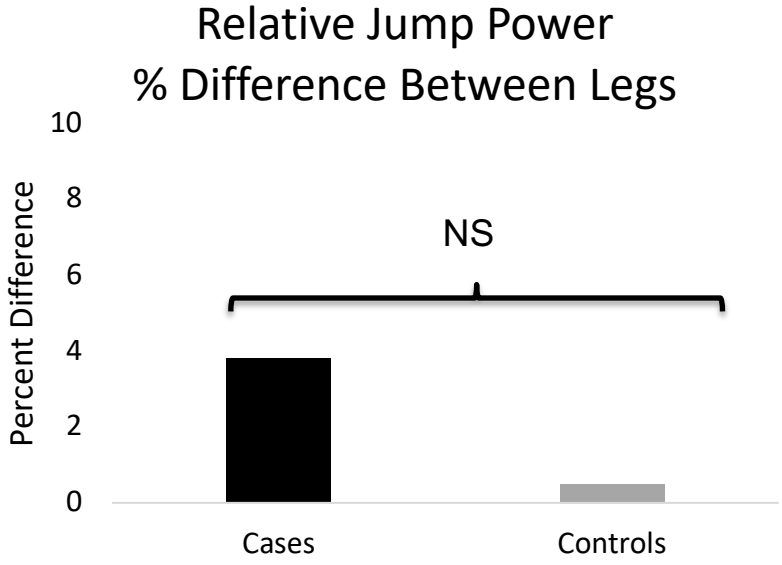

Figure 6: No significant differences were found when looking at the percentage difference in relative jump power between legs and comparing these differences between cases and control groups.

Figure 7: Difference in Total Force Efficiency Between Cases and Controls

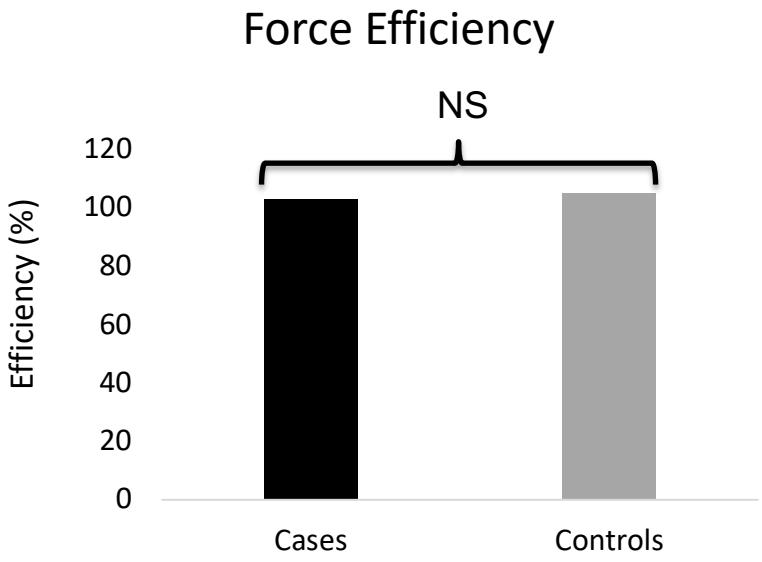

Figure 7: No significant differences were found when looking at the difference in total force efficiency between cases and control groups.

Figure 8: Difference in Force Efficiency Percentage Difference Between Legs

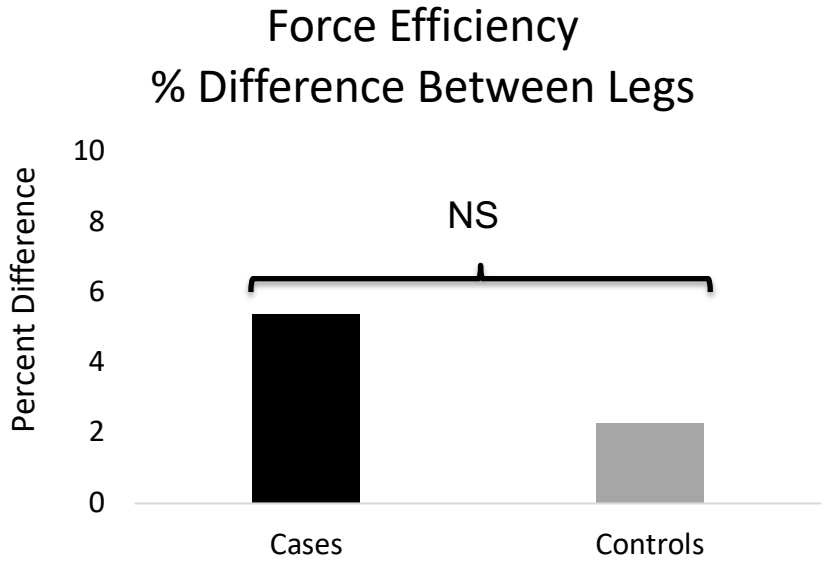

Figure 8: No significant differences were found when looking at the percentage difference in force efficiency between legs and comparing these differences between cases and control groups.

CHAPTER V:

DISCUSSION

The purpose of this present study was to determine whether ACL rupture and reconstruction would lead to any significant changes in subchondral bone density in a repaired knee within 1 to 5 years post-surgical repair. We hypothesized that case subjects would demonstrate significantly greater subchondral bone mineral density, when compared to controls 1 to 5 years following the ACL injury and reconstruction.

The current literature[95-98] provides an array of findings examining changes to bone mineral density following ACL rupture and subsequent repair. A matched case-control study by Zerahn et al. reported significant reductions in bone mineral density and Z-scores in the proximal tibia of the operated leg during the first year following surgery.[95] Two 1-cm^2 regions of interest (ROIs) were placed 2 mm below the medial and lateral subchondral plate of the tibia.[95] Z-Score and bone mineral density values did return to baseline values in the operated knee in all ROIs except the lateral side of the proximal tibia, which still showed a decrease in vBMD 24 months post-operation.[95] These findings led Zerahn to conclude that the initial decline in vBMD after ACL reconstruction may be associated with the relative immobilization after surgery, compounded with the additional trauma caused by the surgical intervention itself.[95] Similarly, a 2013 study by van Meer et al. evaluated 90 subjects who underwent ACL reconstruction, utilizing DXA scans to assess the subchondral vBMD of the proximal tibia. The center of the DXA scanner arm was placed 8 cm below the tibial plateau and

the contours of the femoral and tibial condyles were outlined using active shape model tool kit software from Manchester University.[96] After evaluating subjects at baseline, 1- and 2-years post-surgery, and using linear regression analysis, van Meer et al. concluded that vBMD was significantly lower at the 1-year follow up in all ROIs of the tibia when compared to baseline values.[96] At the 2-year follow-up, vBMD had significantly increased but had not yet recovered to baseline levels.[96] When compared to the contralateral knee, all vBMD findings in all ROIs of the tibia in the injured knee were significantly lower ($P < 0.008$) at all time points.[96] Additionally, Mundermann et al. utilized pQCT and performed a 1 year follow up on ACL-reconstructed knees.[97] pQCT scanner markers were positioned 1cm distal of the medial tibial plateau.[97] They found that by 3 months post-operation vBMD had significantly decreased from baseline values and remained reduced until 12 months following ACL Surgery.[97] With the majority of studies only evaluating 1-2 year post-surgery, Kroker et al. explored the vBMD of subjects who were 5-years post ACL reconstruction. Using pQCT, the authors looked at the subchondral plate of the tibia and found that there was little variability in total tibial trabecular vBMD between ACLR and contralateral knees. Only the medial tibial compartment showed a slight significant increase ($P = 0.016$).

The results of the present study demonstrated that subchondral bone density was significantly greater in cases compared to control groups *(*$P = 0.04$*)*. While these results differ from those reported in other scientific literature it is important to note that Munderman et al. had a shorter interval of 1-year post surgery, compared to the 3.2-year average time since surgery interval of the subjects in this present study. It is plausible that the initial decrease in vBMD is observed due to the large amount of bone remodeling

occurring within the first year after surgery. Following this first year, a compensatory shift occurs were the bone becomes more dense, a theory supported by the results of Zerahn et al. and van Meer et al. who both saw an initial decrease in vBMD in year one and an increase in vBMD in the second year following surgery. Additionally, Kroker et al. only included trabecular bone density in their analysis, while the present study included total subchondral bone density. By analyzing all subchondral bone, the present study was able to assess changes and calcifications of trabecular bone that may have exceeded the threshold generally attributed to trabecular bone. This calcified bone could have been counted as cortical bone and could therefore be excluded or missing from the analysis of previous studies. The specific mechanisms causing these density changes are complex and are still being intensely evaluated by the current literature.

Based on the evaluated literature and the findings of this present study, further research needs to be done to evaluate the long-term effects of ACL rupture and reconstruction on the subchondral bone density of the tibia. The findings of the current study, showed that significantly greater trabecular bone density has been seen as far as 5 years post-surgery in some patient populations. These findings prove to be clinically relevant, as an increase in subchondral bone density is a clear risk factor for increased risk of OA development. With these changes appearing as soon as 1 to 5 years post ACLR, subjects are at a high risk of developing OA at a very young age, decreasing their quality of life and increasing their probability of needing a knee replacement. These findings support that the initial rupturing trauma and surgical intervention may have a greater impact on increases in tibial subchondral bone density than previously suspected. The results of this study warrant further investigation of tibial bone mineral density 5 to

10 years following ACL reconstruction. Further clinical interventions should also be investigated to limit the progression of OA risk factors in young and active populations to starve off OA diagnosis and joint replacement surgeries for as long as possible.

Additionally, we hypothesized that differences in muscle function between the operated and contralateral limbs of subjects may exist 1 to 5 years post-surgery. Such a hypothesis was based on the current literature[99-104], which indicates that subjects could see quadriceps strength and functional deficits as far out as 28 months post ACLR. Curran et al. reported patients who returned to sport activities 6-months post ACLR demonstrated strength and biomechanical scores that were less than 80% symmetrical.[100] At a 12 month follow up, all the strength and biomechanical variables did exhibit improved symmetry between limbs, but only sagittal-plane knee-joint rotation, isokinetic quadriceps index and self-perceived function had reached the standard 90% limb symmetry necessary to be recommended for return to play.[100] Quadricep isometric and isokinetic strength values did not achieve 90% symmetry with the uninvolved limb by 12-months post-operation.[100] Curran et al. concluded that while improvements were made between the 6- and 12-month marks, significant quadriceps strength deficits still existed in these ACL patients 1-year post-operation.[100] A similar study by Kobayashi et al. reported that at the 12-month follow-up mark, subjects still had 27% quadriceps deficit between the involved and uninvolved limbs.[104] While hamstring strength had reached 90% symmetry by 6-months post ACLR, Kobayashi concluded that quadriceps strength could take up to 24 months to achieve the 90% symmetry with the uninvolved limbs.[104] Kobayashi et al. also noted that subjects who experienced anterior knee pain following surgery, and/or utilized a bone-tendon-bone patellar tendon graft experienced a slower

recovery of quadriceps strength.[104] While looking at functional strength deficits in females, Paterno et al. noted significant increases in vertical ground reaction force (VGRF) ($P = 0.001$) and loading rates ($P < 0.001$) in the uninvolved limb during drop vertical jump testing when compared to the involved and control limbs at a mean 27.4 ± 13.8 months following ACLR.[102] The increase of these values in the uninvolved limb demonstrated the involved limb's inability to produce functional strength.[102] Additionally, the involved limbs showed significantly less ability to generated force ($P = 0.03$) when compared to the uninvolved and control limbs.[102] In another study evaluating functional strength deficits following ACLR, Mattacola et al. reported that at 18 ± 10 months post-surgery, single-leg hop for distance scores and quadriceps strength were not within normal limits when compared to the contralateral limb.[103] While the results of the current study did not show any strength differences between the subjects involved, contralateral or control limbs, it's important to note that isokinetic testing was not performed in the percent study.

With regards to clinical significance, Grindem et al. reported that subjects with a limb symmetry index less than 90% were at approximately three times greater risk of sustaining a subsequent knee injury.[105] Limiting strength deficits following surgery, and restoring strength to pre-injury levels before returning to activity are paramount in decreasing an individual's risk of poor knee biomechanics, reduced knee function, and OA development.[99] Buckthorpe et al. identified limiting strength loss after injury and surgery, as well as maximizing and accelerating the recovery of strength after surgery as the two most important strategies to normalize quadriceps strength following ACLR.[99] These two goals should be prioritized by rehabilitation specialists in order to decrease

quadriceps muscle imbalance following surgery. The evaluated literature[99-104] continues to make a very strong case that the currently popular 6-month return to play (RTP) time-line is an insufficient amount of time to allow patients to make the appropriate strength gains to safely resume competitive activity. Based on these findings, further consideration should be given to the 12 to 18-month RTP protocol following ACL rupture. Future research should be aimed at corroborating the findings of this present study and confirm a lack of muscle imbalanced in ACL patients 5 to 10 years post rupture.

Limitations

The present study had a very small sample size, making these results difficult to generalize. Future studies could build upon these results by looking to increase study recruitment and participation. Further limitations include the lack of available pre-injury data for the case group. No baseline vBMD values were able to be obtained from case-patient's immediately following surgery. Future studies should look to investigate the reported decrease in vBMD 1 to 2 years following ACLR. These decreases have been reported in many, well-designed research studies and further investigation should be done to assess whether these vBMD decreases rebound into the increases seen in this current study. Further evidence investigating the impact of ACL rupture and repair on bone mineral density and muscle strength 5 to 10 years post-surgical intervention is critical to OA research and prevention.

Additional limitations to this study include the possibility for control subjects to have experienced previous knee trauma that was not reported in pre-study participation screening. A small number of self-reported meniscus tears were disclosed by case subjects. We were not able to investigate the effect of graft type on any changes to subchondral bone density. Movement efficiency, changes in force, power, and ground reaction force production were all assess used only Leonardo Mechanography. Future studies should look at including isokinetic strength values. EMG could be included in future studies to provide an additional variable for analysis. Lastly, joint alignment was not measured in either the control or case groups and is a value that could be included in future research.

Conclusion:

This study aimed to determine whether ACL rupture and reconstruction would lead to any significant changes in subchondral bone density, in a surgically repaired knee, within 1 to 5 years post-intervention. The results of this study did confirm the established hypothesis that case subjects would demonstrate greater subchondral bone density when compared to control subjects and uninjured limbs. Based on the results of this present study, we concluded that significantly greater subchondral bone density could be seen within 1 to 5 years following ACLR, in the patient's reconstructed knees. These findings confirm suspicions that the rupturing force of the ACL injury, the surgical repair intervention and the recovery process could also contribute to increases in subchondral bone density and the risk of OA. While these results were found to be significant, further research should be conducted to substantiate these findings.

APPENDICES

APPENDIX A

Participant Consent Form
Participation in a Research Project
South Dakota State University
Brookings, SD 57007

Department: Ethel Austin Martin Program in Human Nutrition

Project Director: Lee Weidauer Phone Number: 605-688-4630

E-mail: Lee.Weidauer@sdstate.edu Date:

Please read (listen to) the following information:

1. This is an invitation for you to participate in a research project under the direction of Dr. Lee Weidauer.
2. The project is entitled "Subchondral Bone and Muscle Function Changes Following ACL Reconstruction".
3. The purpose of the project is to determine if changes in the bone directly below the cartilage in the knee changes following ACL repair and to what extent muscle function may plays in these changes.
4. If you consent to participate, you will be involved in the following process that will take about one hour of your time. On the day of your study visit, you will report to the Ethel Austin Martin Program's mobile bone research unit. The study visit will consist of questionnaires, height and weight measurements, jump testing, and bone measurements.

Questionnaires

You will be asked to fill out a health history questionnaire that will ask about your overall health and any chronic medical conditions you may suffer from. Additionally, you will be asked for a detailed orthopedic health history. This will be done to determine whether or not additional factors are present that could potentially affect subchondral bone.

Height and Weight

Height and weight without shoes will be measured 2-3 times using standard procedures. Height and weight are known predictors for bone measurements.

Medical Records

If you have had ACL surgery, we will ask that you sign a medical record release form that will allow us to request information about your surgery from the facility that performed the operation.

Jump Testing

Ground reaction force and movement efficiency will be measured using a force plate. For the first test, you will be asked to stand on the force plate and jump on two legs as high as you can. You will be asked to do this three times. The next test will be similar, however, you will be asked to perform the jumps on one leg. The results from these tests will be used as a measurement of muscle function.

Bone Measurements

Subchondral bone refers to the bone that is underneath you knee cartilage. The density of this bone will be measured using a technology called peripheral quantitative computed tomography, or pQCT. During the pQCT scans, you will be asked to sit motionless in a chair with your leg in the machine.

5. Participation in this project is voluntary. You have the right to withdraw at any time without penalty. If you have any questions, you may contact the project director, Dr. Weidauer, at the number listed above.
6. The risks involved with your participation in the study are considered very minimal. During the pQCT scans, you will receive a small amount of radiation exposure. The exposure will total 2.8 millirems, which is less than an airline flight across the United States or a standard chest x-ray (5 millirems). Even though the risks are minimal, please notify study staff if there is a chance you may be pregnant. If there is a chance you are pregnant, you will be offered a free pregnancy test and if the test is positive you will no longer be eligible to participate.
7. There are no direct benefits to you for participating in this study.

8. Your responses are strictly confidential. When the data and analysis are presented, you will not be linked to the data by your name, title or any other identifying item.

As a research participant, I have read the above, have had any questions answered, and agree to participate in the research project. I will receive a copy of this form for my information.

Participant's Signature _____ Date _____

Project Director's Signature _____ Date _____

If you have any questions regarding this study you may contact the Project Director. If you have questions regarding your rights as a participant, you can contact the SDSU Research Compliance Coordinator at (605) 688-6975 or SDSU.IRB@sdstate.edu.

This project has been approved by the SDSU Institutional Review Board, Approval No.: IRB-XXXXX-EXP

APPENDIX B

MEDICAL HISTORY QUESTIONNAIRE

Name:_____Participant ID:_____Visit Date:_____

Are you currently taking any medications (initial visit only)? YES NO

If Yes, please list below.

Medication	Reason

Do you have any of the following conditions (*Circle all that apply)*

Acid Reflux (Heartburn)	Chronic Low Back Pain
Alcoholism	Depression
Allergies	Diabetes Type 1
Anxiety	Diabetes Type 2
Asthma	High Blood Pressure
Atrial Fibrillation	Irritable Bowl Syndrome
Cancer	Migraines
Coagulation (bleeding) problem	Low Bone Density or Osteoporosis
High Cholesterol	Thyroid Problem
Heart Disease	Kidney Disease
Blood Clots	Osteoarthritis

Tuberculosis	Rheumatoid Arthritis
Emphysema	Anemia
Hernia	Muscular Dystrophy

Please list all surgeries that you have had in the past 5 years.

Surgery	Year

Do you currently use tobacco (Initial Visit Only)? YES NO

Do you currently use alcohol (Initial Visit Only)?
(circle the response that best describes your alcohol use)

NEVER RARELY (1-2 Drinks/month) SOCIALLY (1/week most weeks) F

APPENDIX C

DATA COLLECTION FORM

Name:_____DOB:_____Participant ID:_____

Telephone Number:_____Email Address:_____

Height:_____Weight:_____

Is there any chance you may be pregnant? YES NO MALE

Have you ever had an ACL reconstruction? YES NO

What kind of graft was used during the procedure? _____

pQCT Testing

CT Number: Left_____Right_____

Mechanography

Peak force double leg:_____

Peak force left leg:_____

Peak force right leg:_____

APPENDIX D

South Dakota
State University

Patient Information:	Name:_____ DOB:_____ Address:_____ City/State/Zip:_____ Social Security Number:_____
Provider:	Physician:_____ Facility:_____ Address:_____ City/State/Zip:_____
Disclose Information To:	Dr. Lee Weidauer E.A. Martin Program in Human Nutrition SWC Box 506 South Dakota State University Brookings, SD 57007 Phone: 605-688-4630 Fax: 605-688-4220
Information to be Disclosed	Physician notes, radiology reports, surgical summaries, and rehabilitation notes. regarding the patient's anterior cruciate ligament injury, surgical repair, and subsequent rehabilitation.
Service Dates:	Time period from _____ to _____ Information regarding an injury to the anterior cruciate ligament and all related treatments
Purpose of Disclosure:	Research project investigation changes in subchondral bone following ACL repairs.
Expiration Date:	This authorization will expire one year from the date of the signature.
Revocation:	I understand that I may revoke this authorization at any time by sending a written notice to the health care facility noted above. However, the revocation is not valid if (1) action was previously taken in reliance with this authorization, or (2) this authorization is obtained as a condition for obtaining insurance coverage; other law provides the insurer the right to contest a claim under the policy.

Authorization: I herby authorize the above facility/provider to disclose medical information concerning the above named patient to the party identified in the section entitled "Disclose Information To". I understand that once the information is disclosed, it may be subject to re-disclosure by the recipient and may no longer be protected. I understand that this authorization is voluntary and that I may refuse to sign this authorization.

Signature of patient	Signature Date
Signature of study personnel	Signature Date

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