Bone Geometric Adaptations and Functional Outcomes after ACL Reconstruction: Cross-sectional and Prospective Observations

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Dedication

To my parents, my sister and brother-in-law, my family and friends for their enduring love and encouragement through this long broken road. And of course, my Simba, the lion king.

I tried making good on that promise
Thought I'd be so much further by now
But I've had the best of intentions from the start

Now some people think I'm a loser
Cause I seldom get things right

It was all with the best of intentions

Travis Tritt- Best of Intentions

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1

RATIONALE, SPECIFIC AIMS, AND HYPOTHESES

1.1 Rationale

Anterior cruciate ligament (ACL) tears are a fairly common injury among professional and recreational athletes (1) as well as nonathletes, with an estimated 250,000 ACL ruptures occurring in the US each year (2, 3). After ACL surgery, immobilization and disuse are inevitable, which cause a decrease in mechanical load for the ACL patient. Understanding the effect of ACL reconstruction and subsequent change in mechanical load on bone and muscle may have important implications for neuromuscular function, athletic performance, and may increase risk of osteoporosis related fractures and musculoskeletal disease in later life (4-10).

According to the well-established mechanostat theory, changes in mechanical load is the primary factor to which bone adapts its strength (11). Loading and disuse studies in animals support the theory that bone strength adapts appropriately to changing mechanical loads (12-14). In the human literature there is a lack of ACL studies exploring changes in bone strength with disuse or unloading (15). Most of the ACL studies (16-19) have focused on bone mass and areal density as primary outcomes; however, today's technology allows the study of other variables that are important contributors to bone strength.

Customary loading becomes absent after ACL injury and repair due to pain, swelling, instability, and the danger of more musculoskeletal damage. In an ACL transected limb, loading is reduced to ~35% of preoperative levels 2 weeks after surgery and slowly increases to 50 – 60% within 6 – 12 weeks (20, 21). Data has shown that the average nonweight-bearing time after reconstruction is 1.9 weeks and an additional partial weight-bearing time is 2.4 weeks (22). Thus, ACL reconstruction provides a clinical model for exploring the bone and muscle adaptations to acute unloading.

Dual energy x-ray absorptiometry (DXA) based studies on ACL reconstructed patients have shown decreased bone mass and areal bone mineral density (17, 19, 22, 23). These ACL studies lack the assessment of the structural parameters of bone, which are important when determining the strength of a bone (24-28). Bone may alter it's strength by changing not only mass and density, but also geometry and structure. The ability to measure bone volumetric density, bone geometry and estimates of bone strength are now possible due to the advancement in technology.

In this dissertation, I explore the musculoskeletal consequences of ACL surgery. From a theoretical perspective, ACL reconstruction provides a strong human model to explore bone adaptation to disuse. From a clinical perspective, this study will further knowledge on the bone, muscle, and functional adaptations to ACL reconstruction. This thesis will address several gaps in the literature:

1) Exploring the effect of ACL surgery on muscle and bone may have significant implications for optimizing musculoskeletal health. Age, gender, physical inactivity and immobilization are all risk factors for osteoporosis (29-31) and are also characteristics associated with ACL reconstruction. As a consequence of osteoporosis, fractures are of greatest concern due to major medical complications and mortality (32). Also, related to ACL injury, being an athlete may be a risk factor for osteoporosis. An injury along with a sudden termination of sport-specific loading will produce a drastic change in the musculoskeletal system compared to a non-athlete (19). Some researchers have suggested that posttraumatic osteopenia and the risk of fractures in later life may be unavoidable despite proper prevention and rehabilitation efforts in patients with ACL injury or reconstruction (16, 19). However, these suggestions were based on prior studies that explored bone changes after ACL reconstruction with 2 dimensional imaging techniques, which only measured bone mass or areal density (16-19, 22). Bone mass and density create an incomplete picture of a bone's strength, since a decrease in BMD does not necessarily equal a decrease in strength (33). Mechanical properties of bone such as bone volumetric density, geometry and estimates of bone strength are needed to determine if ACL injury along with a reconstruction pose a true risk of posttraumatic osteoporosis. Therefore, there is an obvious need for studies in patients with ACL reconstruction that assess these important bone geometric properties and estimate bone mechanical strength.

2) Mainly animal (7, 8, 34, 35), but also human (18) studies have reported that the greatest bone losses nearest the injury appear to be in the trabecular bone and below the subchondral plate. As a result, microfractures may occur that could lead to the

congruence of the joint surface to adapt, which causes altered stresses in the knee joint along with subsequent degenerative joint disease (6). The literature has reported that almost all patients acquire radiological indicators of osteoarthritis (OA) 15 – 20 years post surgery (36). A previous study (37) demonstrated that six weeks following surgery, gait characteristics became highly different compared to those of the healthy control group. ACL reconstructed subjects produced a highly different tibial translation. No significant differences were found 8 months after reconstruction. Assessing distribution changes in bone volumetric density, geometry and estimates of bone strength may aid in understanding the posttraumatic pathogenesis of osteoarthritis in ACL patients.

3) Despite the vast clinical and research interest in ACL injury and reconstruction, there are few published studies aimed at long-term functional ability. The few studies (9, 38, 39) that range from 6 - 10 years post surgery and 24 years post (40), focus on comparing functional outcomes between different donor sites. A limitation of these studies is that they assess function primarily using questionnaires and do not directly assess function or use only the single leg hop test (9, 38-40). Some authors have proposed that the single leg hop test is not a sensitive enough measure of function in this population (41-44).

The main objective of this dissertation is to explore the muscle, bone and functional adaptations after ACL reconstruction via measures of bone volumetric density, geometry and estimates of bone strength. This thesis consists of 3 manuscripts. The first paper, a cross-sectional study, explores the effect of previous ACL reconstruction on bone strength and muscle size of the surgical and non-surgical legs. In the second manuscript, I prospectively observed muscle and bone outcomes before and after ACL reconstruction. The final paper addresses both subjective and clinical functional outcomes in patients with a history of ACL reconstruction; and explores a clinically useful test of function in this population (retro step test).

1.2 Specific Aims and Hypotheses

Specific Aim 1: To explore the effect of ACL reconstruction on bone strength and muscle size of the surgical compared to non-surgical legs.

The *working hypothesis* for this aim, The *working hypothesis* for this aim is that bone strength will be significantly lower in the surgical compared to non-surgical legs 1-5 years post surgery at sites nearest the injury (proximal tibia, patella and distal femur), whereas sites further from the injury will have no differences between the surgical and non-surgical legs. The *secondary hypothesis* is that there will be no differences in muscle size between the surgical and nonsurgical legs.

These hypotheses have been based on prior human and animal literature:

Previous studies (37) have shown that activity of muscles appear to return to normal 8 months post-surgery, whereas muscle strength does seem to return to pre-op levels over time, typically between 1 – 2 years after surgery (45-47). Frost (48) suggested that after the fast adaptations of muscle there is a lag before the sluggish responses of bone are seen.

Both the animal and human studies performed to date reach a similar consensus that BMD decreases at the sites closest to the injury (7, 8, 16, 17, 22, 23, 49, 50). The greatest bone losses nearest the injury appear to be in the trabecular bone (8) and below the subchondral plate (18). A decrease in cancellous BMD and subchondral bone has been suggested to decrease bone strength (6). Regardless of suitable rehabilitation actions, prior studies (16, 18, 19, 22) have not been able to determine if the change in BMD after ACL reconstruction has truly decreased the strength of the bone. An increase in stresses on bone such as rehab and exercise causes an outcome of bone formation (mechanostat theory), typically periosteal apposition, which expands the periosteal diameter and increases strength.

Specific Aim 2: To explore *changes* in muscle size and bone strength for 9-months following ACL reconstruction.

The *working hypothesis* for this aim is that bone strength will continue to decrease at sites nearest the injury (proximal tibia, patella and distal femur) through 4-months. The *secondary hypothesis* is that muscle cross-sectional area will also decrease over 4-months post surgery.

These hypotheses are been based on prior human and animal literature discussed briefly below and highlighted in detail in the literature review.

Immobilization induced bone loss is at greatest during the first 6 weeks (51-53) post injury, and typically reaches a steady-state at 6 months post injury (51, 53). A standard bone remodeling sequence takes around 3 -4 months and may not be accurately represented in measurements or fully mature until 6 – 10 months (54, 55).

Previous studies suggest that at 6 months post-surgery the surgical leg has 25-36% lower muscle strength than the contralateral limb (46, 56, 57). A clear improvement in muscle strength was noticed between 6 and 12 months post-surgery. Similarly, other studies have demonstrated that muscle electromyographic activity appears to return to normal 8 months post-surgery (37).

Specific Aim 3: To describe both subjective and clinical functional outcomes in patients with a history of ACL reconstruction as well as explore clinically useful tests of function in this population.

The *working hypothesis* for this aim is that there will be approximately 30% of our participants who score below normal on functional tests and subjective questionnaires. The *secondary hypothesis* is that the retro step test will be more difficult for a greater number of participants than the standard functional tests.

These hypotheses have been based on prior human and animal literature:

Overall, there is a lack of long-term data with direct assessment of functional outcomes in patients with a history of ACL reconstruction. To fully capture the ability to return to play as well as activities of daily living, muscle strength and clinical and functional outcomes are commonly measured on ACL patients. The ability to perform functional tests of the lower extremity within normal values is regarded as an important criterion (58).

Noyes et. al. (59) recommended the law of thirds for individuals treated with rehabilitation for their chronic ACL injuries. For example, one third of the individuals will recommence their prior physical activities without surgery, one third alter their activities to avoid reconstruction and the last one third of patients need an ACL reconstruction since activities of daily living are impossible to do without giving-way episodes. Thus, an ACL patient has a 33% chance of being a coper, compensator or noncoper.

Researchers have proposed that subjects who are further post-surgery may have some degenerative changes such as periarticular osteopenia, cartilage degradation, joint space narrowing and thickening of the subchondral plate (7, 34, 60), which may account for participants scoring below normal on functional tests. Therefore, subjects who are only ½ a year to a 1 ½ post-surgery may have better function than those 10 years post-surgery. However, subjectively it appears that as time increases, patients feel better regarding their overall knee function (61).

The retro step test (62) is commonly used to diagnose patello femoral pain (PFP) (63, 64) but has not been traditionally applied to ACL patients. The retro step requires the high demand of balance and stability as well as the motor ability to step backward at increasing heights.

2

LITERATURE REVIEW

Introduction

An estimated 250,000 ACL ruptures occur in the US each year and the number of surgical reconstructions performed each year total over 100,000 (2, 65). Studies of ACL injury have mainly focused on clinical and functional outcomes and prevention programs. However few studies have focused on the role of gender and age of surgery on functional outcomes. In addition, ACL reconstruction also provides a unique clinical model to test the Mechanostat theory (66). The mechanostat theory expresses the active regulatory process whereby bone is adept to react to its mechanical environment. For example, increasing bone strength when subjected to larger than normal loads (overload) and exonerating bones of unnecessary mass when exposed to reduced loads (disuse). As a disuse model, studies of ACL injury and reconstruction have reported bone and muscle loss. These studies only report measures of bone mass and density. Therefore, further research is needed: 1) to clarify functional ability and subjective satisfaction post ACL reconstruction, and 2) to explore bone geometric adaption post ACL reconstruction.

The review of literature is divided into 3 main parts. First I provide a background on the epidemiology and clinical history of ACL injuries including treatment and functional assessment. The second section focuses on bone biology, biomechanics and muscle physiology. In the final section I review the most relevant literature manuscripts comprising ACL and bone, ACL and muscle and ACL and muscle-bone.

2.1 PART I: Background

2.1.1 Epidemiology and clinical history

The ACL is a stabilizer, which links the upper and lower leg.

The ACL is a primary restraint and is necessary for stabilizing in pivoting actions. Without a healthy ACL, the tibia could turn beneath the femur in an anterior-lateral path. This happens mainly when an action such as pivoting, an abrupt deceleration or landing from a jump is intended (1). The ACL and posterior cruciate ligament (PCL) support flexion and extension actions as well as sliding movements. The ACL is approximately 30 – 40 mm long and 11 mm wide (67), it is a stabilizer that links the upper and lower leg and prevents excessive anterior translation of the tibia in addition to supporting rotational and pivoting movements. The tibial attachment sits slightly medial to the lateral meniscus attachment, from there the ACL continues to proceed posteriorly and superiorly to the intercondylar notch on the femur, posterolateral side. Several researchers (68-71) have expressed that the ACL has two separate fiber bundles based off the tibial attachments. The anteroposterior dimension of the ACL is roughly 17 $\pm$ 2 mm and the medial lateral width is about 9 $\pm$ 2 mm (67). These fiber bundles appear to be 'functional,' meaning that tension can vary along the bundles throughout the range of motion. When the knee shifts from extension to flexion, the ACL fibers twist (69). Thus, in extension the posterolateral band is tight, while in flexion the anteromedial band tenses and the posterolateral band loosens.

After suffering a knee injury, most individuals will visit a sports medicine professional.

As imagined, most ACL ruptures are quite painful, particularly within the first couple of minutes (1). Commonly, athletes will not be capable of maintaining their activity. Occasionally, hemarthrosis (large tense effusion), minimal or delayed swelling or both will occur. Often the athlete will attempt to re-enter the activity; however, the individual will feel a lack of confidence and instability in the knee.

After an ACL tear, most individuals visit a sports medicine professional around 24 – 48 hours post-injury. At that time point, the knee is quite difficult to examine due to hemarthrosis, swelling and pain. The best stage in which to examine the knee is within the first 60 minutes of injury. At the examination, the individual will explain that they heard a pop, snap, or tear, they felt movement within the knee, clicking or locking, and the knee giving way (1).

Physical exam tests such as the Lachman's test (72), positive pivot shift test (1), and the anterior drawer test (1) may be performed. The Lachman's test will be positive in a patient that has torn their ACL, and is the best test for this injury. Imaging tests such as an x-ray or MRI may be performed as well. Common features noticed at the examination of a torn ACL include: restricted movement, mainly deficits in extension, widespread moderate tenderness, especially the lateral side (subluxating), and additional medial joint tenderness if the medial meniscus was also damaged.

Non-contact ACL injuries are more common than contact ACL injuries.

Contact ACL injuries are commonly precipitated by a rapid deceleration, a sudden change in direction, a collision with a varus or valgus shearing mechanism stress applied to a side of the knee, hyperextension or a blunt blow or clipping action in a sliding/tackling maneuver (73, 74). Multiple structural damages are often produced from a contact ACL injury such as the medial meniscus and the medial collateral ligament (O'Donoghue's Triad).

Over half (60-80%) of the ACL injuries that occur are by non-contact mechanisms. Interestingly, it can result from a movement that the individual has completed many times. An abrupt deceleration, sudden change in direction, and knee flexion between 20 degrees to full extension or hyperextension may lead to an ACL injury. Injury during ball sports are usually caused by a cutting maneuver (75-77) or one leg standing. A cutting move will cause increases of internal rotation or varus-valgus actions. External factors may also play a role such as being pushed or held, off balance, avoiding collision, fatigue, loss of concentration, inadequate muscle protection, poor neuromuscular control (78) and wider than normal foot position, which causes the foot to plant. As a result, the lower extremity is not favorably aligned.

Additional culprits of ACL failure are an eccentric contraction in the quadriceps, knee collapse inward to the hip and foot and internal rotation with the knee flexed more than 90 degrees (79). Skiers that have ruptured their ACL most likely occurred because the tibia internally rotated while the knee was flexed more than 90 degrees (80). Both the quadriceps and the hamstrings are key dynamic stabilizers for the knee, which significantly regulates the anterior dislocation of the tibia (81).

Core stability is typically characterized as dynamic control of the trunk that permits production, transmission, force and motion to lower components of the kinetic chain (82). If one's core has deficient neuromuscular control during athletic movements, uncontrolled trunk displacement is likely. As a result, the lower limb may be subjected to a valgus stance and increased abduction and torque movement in the knee that can result in knee ligament strains or an ACL rupture (83-88). Previous studies (89, 90) have shown frequently that muscle activity in the trunk occurs ahead of muscular activity of the lower extremity. These authors proposed that a stable foundation is established by the central nervous system for lower extremity movement by the transverse abdominis with the teamwork of the multfidus muscles (89). Neuromuscular training studies have supported this theory by demonstrating that when core stability exercises were incorporated, knee injury risk was decreased (91, 92).

Houck et. al. (93) studied an anticipated and unanticipated side step cutting task. They observed a lateral shift in the thorax's center of mass and a medial translation of the hip, which caused a lower moment of knee abduction. The authors suggested that athletes may need to modify functions of the hip musculature that influence the knee. Larger knee adduction moments were correlated with hip internal rotation and flexion as well as knee abduction angles when performing a side step cut (76). However, neither anticipation nor trunk position effects were assessed in this study. Other studies have shown additional support for the relationship between the hip and knee (94). Subjects without injury demonstrated significantly greater hip abduction and external rotation. According to the regression analysis, the only helpful variable for predicting injury was hip external rotation strength.

2.1.2 Risk factors associated with ACL injury in women

Females have a much greater chance of an ACL injury (2.4 - 9.7 times higher) (95-99) in certain sports than their male counterparts. Several studies have focused on ACL injuries in female athletes (100-105). From these studies, risk factors have been categorized as *intrinsic (hormonal, anatomic, neuromuscular) or extrinsic (environmental, biomechanical*). Uhorchak et. al. (106) created a risk equation for ACL injury overall. The strongest predictors were the female gender, smaller intercondylar notch width, greater body mass index and knee joint laxity. Below I discuss the factors that are generally thought to explain the higher risk for ACL injury in females.

Hormonal milieu

Ligament laxity, collagen synthesis and fibroblast proliferation in the ACL seem to be influenced by hormones. It has been shown that the ACL has receptors for hormones (estrogen, progesterone, relaxin) that are involved in the menstrual cycle. Some researchers believe that ACL laxity and injury are influenced by estrogen (101, 105, 107-109).

Experiments examining the association of ACL injury and the menstrual cycle have been conducted, unfortunately, there is a lack of consensus (95, 107, 108, 110-112). Researchers have also investigated and implicated inflammatory mediators and matrix metalloproteinases along with their inhibitors (113). An experiment by Cao et. al. (114) demonstrated that internal mechanisms can directly influence the matrix and healing ability of the ACL after injury.

Anatomical

Males and females have anatomical differences. The intercondylar notch of females are not the same shape as males and are smaller in size (115, 116). Females have been shown to have wider pelvis's, which creates a greater Q angle, an increased femoral anteversion, greater genu valgum, and asymmetries.

Neuromuscular

Neuromuscular differences between the genders appear to involve the hamstrings (117), quadriceps, and proprioception. It is crucial that the hamstrings and quadriceps have balanced power and recruitment or knee instability is likely. Instability typically results from unregulated rotation of the leg beneath the pelvis during pivoting and landing, and controlling the functional valgus knee. It has been reported that females depend more on their quadriceps (118). This means the quadriceps are activated first instead of their hamstrings in reaction to anterior translation (118). Eccentric contraction in the quadriceps can generate loads more than those required for tensile malfunction of the ACL (119). Conversely, males tend to activate their hamstrings first, which dynamically steadies their knee and avoids displacement of the tibia (120). Another neuromuscular difference noticed between males and females is the distinction in timing of their muscle firing patterns (91).

Environmental factors

Environmental factors examined by researchers include the weather, shoe surfaces and playing surfaces. Scientists have found that friction coefficient rate (121, 122) position of cleats (102), rainfall and type of grass (123) can all influence the incidence of ACL injury. It appears that rye grass tends to be a safer surface than other grasses (124). Wooden floors, which are known to have lower friction were compared to artificial floors that are known to have higher friction (122). Results showed that risk of injury was greater on high friction floors than low friction floors for female handball athletes.

Biomechanical

Biomechanical differences between men and women also seem to be a reason for the greater incidence in females tearing their ACL. One experiment studied female loading strain patterns compared to male loading strain patterns using a knee cadaver model. Their data revealed that the loading strain pattern on the ACL for females was significantly greater ($p<0.05$) from the posterior tibial shear force compared to the males. It appears that the motor control patterns for females place greater loads on the ACL versus the males ACL (125).

Another study examined landing from a jump, comparing gender and biomechanical peak values. Females demonstrated greater peak knee valgus (9 degrees more; $p = 0.001$) when landing from the jump as well as extensively greater maximal ground reaction forces (140%; $p = 0.003$) versus the males. These researchers proposed that the greater peak knee valgus and ground reaction forces potentially are reasons for females having a greater risk off ACL injury. Possibly improving knee valgus control and decreasing ground reaction forces will help decrease the number of ACL injuries seen in females (126). Additionally, females appear to have greater knee (127-130) and hip (129) extension in the landing position, which creates the higher forces felt by females (127).

2.1.3 Treatment of ACL injuries

The choice of treatment will be different from individual to individual. Whether the ACL patient chooses non-surgical or surgical treatment, active rehabilitation should start as soon as possible (131). The goals of active rehabilitation include decreasing pain, diminishing the magnitude of fibrosis, and maintaining and improving ROM, muscular strength (quadriceps, hamstring, hip extensors and abductors and the calf's) and function. At first, anti-inflammatory drugs and physical therapy can be utilized to decrease synovitis and progress the individual's ROM. Once the inflammation has dropped, the method of treatment can be decided.

More than 100,000 ACL reconstructions are completed each year in the United States (132). To date there is no set criteria for an individual to have or not have an ACL reconstruction. Current information has taught us that surgical reconstruction is not a requirement for all individuals who tear their ACL. The deduction that normal knee function is not capable without an ACL, that a torn ACL causes degeneration in the knee, and that surgery will achieve the restoration of normal function have all been reported as rationale for ACL surgery. Many authors agree that a high intensity lifestyle that includes heavy work or sports with pivoting and decelerating or there are other significant knee complications (meniscal tears, cartilage damage, significant laxity, recurring incidences of giving way), are most likely best served by surgery (98, 133-135). Conversely, authors (136-138) have demonstrated a lack of correlation between the amount of knee laxity and physical tests. Ferrari and Bach (139) suggested that using an arthrometer to measure laxity is not a significant indicator for ACL reconstruction. A 1999 survey of members of the American Orthopaedic Society for Sports Medicine (N = 742) reported that the vast majority of surgeons treated ACL tears with reconstruction rather than with non-operative treatment (98, 136, 140, 141).

In contrast, the assumption that the ACL ruptured knee can reasonably function during most circumstances and that surgery does not necessarily stop the onset of osteoarthritis have been reported as rationale for non-surgical treatment (98, 133-135). It has been suggested that individuals who have minimal exposure to high-intensity activities, are willing to pass up pivoting sports, are 40 years old or more, are successful at adapting and coping to injury, have significant arthritis in the knee and are unlikely to fulfill a rehabilitation program are good candidates for non-surgical treatment (142). It is important to note that individuals that return to high-intensity activities have been known to do well, without an ACL reconstruction (98, 133, 141, 143).

Myklebust et. al. (36) completed a follow-up 6- to 11-years post-ACL injury in 86 handball players. Their study demonstrated that 91% of the elite handball players treated non-surgically were able to compete at pre-injury level. In contrast, only 58% of those who underwent a reconstruction were capable of playing at their pre-injury level. These results are comparable to other experiments as well (144, 145). Together, these investigations provide evidence that with early activity alterations and neuromuscular therapy, an ACL patient can avoid deterioration in the knee and possibly elude late ACL reconstruction.

Each donor site has advantages and disadvantages.

If an ACL patient selects reconstruction as part of their treatment, s/he will need to choose a type of graft. The most commonly used grafts are the hamstring autograft, an allograft and the patellar tendon autograft.

Bone-Patellar-Tendon-Bone

Although some studies have found no differences in outcomes among graft types, there are a number of investigations that have found different results post-reconstruction. The patellar tendon graft or bone-tendon-bone (BTB) graft is thought to obtain superior results due to its high tensile strength of accessible tendons surrounding the knee and permits bone-to-bone fixation at insertions sites. These advantageous of the BTB graft result in greater and earlier fixation strength and does so without sacrificing a significant knee stabilizer (3, 146). Noyes and colleagues (147) were able to demonstrate that the strength of the patellar tendon autograft was 159-168% of the native ACL. Another positive for the BTB graft is A-P laxity. A-P laxity has been shown to be closer to normal values in BTB patients compared to hamstring grafts (99, 148, 149), which has been demonstrated to continue as much as three or more years following surgery (99, 150). Feller et. al. (150) reported A-P knee laxity values for the hamstring group were > 3 mm in 10% more subjects than the patellar tendon group at three years post-reconstruction. The demonstrated strength of the BTB graft and procedural developments and normal A-P laxity values are reasons for this grafts choice popularity among orthopedic surgeons (3).

Conversely, patients receiving a patellar tendon graft tend to have significantly greater kneeling discomfort and anterior knee pain (99, 151, 152) as well as lack of full knee extension compared to the non-surgical side (153, 154). Other disadvantageous of the BTB graft are demonstrated greater deficits in knee extensor strength at the 4 and 8-month measurement following surgery (150) and osteoarthritis has been shown to occur at a higher incidence compared to the hamstring graft (9).

Hamstring

The main benefits associated with choosing the hamstring graft appears to be a lower incidence of patellofemoral crepitus and a lower chance of knee extension loss (99). In addition, anterior knee pain is significantly less in hamstring patients (151, 152) versus patellar tendon patients. However, reports suggest that choosing a hamstring graft means a patient will most likely demonstrate significant deficits in knee flexor strength (150, 155). Not secured with bone at both ends like patellar tendon.

Allograft

Another viable option that has been advocated for ACL reconstruction and has been used for the last 20 – 30 years is an allograft. Enticing advantages of allografts include decreased operative time, decreased morbidity, lower prevalence of arthrofibrosis, preservation of flexor and extensor strength and ROM, faster return to daily activities, and an improved cosmetic look (45, 99, 156). Also, some individuals may not have a graft source to give or a bigger graft may be needed. On the negative side, an allograft costs more, may not be available, and the structural properties may be altered due to sterilization and storage processes. The subject will also be at risk for infection and tunnel enlargement as well as sluggish or unfinished incorporation and remodeling, and an individual's immune response (99, 157-159).

A number of studies (9, 99, 150, 160, 161) have demonstrated no differences in clinical and functional outcomes following surgery between the patellar tendon graft and the hamstring graft (semitendinosus or combined semitendinosus-gracilis tendon) up to 6 years post-surgery. The outcomes consisted of 1) knee extension and flexion strength; 2) range of motion (ROM); 3) A-P knee laxity; 4) anterior knee pain; 5) return to pre-injury activities; 6) 1-legged hop test; 7) patellofemoral pain; 8) jumping, cutting, and pivoting; 9) and the KOOS, IKDC, Cincinnati knee score, Lysholm score, and Tenger activity level questionnaires. It has been reported that of patients with a patellar tendon reconstruction and a 4-strand hamstring graft, 97% and 100%, respectively, rated their results as either good or excellent (9, 111, 150, 160, 161). Although radiographs demonstrated significant tunnel widths in the femur and tibia for subjects with a hamstring graft versus a patellar tendon graft, a 2-year follow-up reported no differences in clinical and functional outcomes (151). These results are supported by a 2004 published review that revealed no differences between the patellar tendon graft and the hamstring graft in failure rate, ROM, and isokinetic strength (162). Thus, it has been proposed that successful results following ACL reconstruction may not be due to the graft type received (163).

The optimal timing of ACL surgery is not conclusive

There is no agreement of position as to the ideal time to undergo ACL reconstruction. Initially, it was ordinary for the individual to have surgery as soon as practical or within 7 days of the injury. Some physicians suggest that having surgery early will keep knee laxity closer to normal and the chance of meniscal and cartilage damage lower. However, full ROM was not returning to normal for some patients. Surgeons began to propose that reconstruction should be postponed in order to reduce the likelihood of arthrofibrosis (59). Originally, a three-week delay in surgery was suggested. Results have shown good reports for both early and postponed ACL reconstructions (164). Unfortunately, most of the data is retrospective and there is no universal definitions for terms such as acute and chronic.

A prospective study by Hunter et. al. (165) evaluated motion and knee laxity in subjects who had ACL reconstruction within two days of injury, 3 – 7 days post-injury, within 1 – 3 weeks of injury, and greater than 3 weeks post-injury. Both motion and knee laxity were found to be unrelated to the timing of reconstruction. Interestingly, quite a few patients who had surgery within 3 weeks of their tear required additional surgical treatment for complications such as decreased motion versus those subjects that postponed surgery for greater than 3 weeks. Although this study was informative, the subjects were not randomized, the individuals chose their time frame, and surgical procedures were not the same for everyone.

It has been stated that pre-surgery ROM should be the same as the non-injured knee and minimal knee swelling are more imperative than the timing of reconstruction. Thus, the condition of the knee is the vital component for making surgery decisions. Until ROM is normal, the swelling is gone and normal gait is achieved, the patient should be participating in active rehabilitation before surgery. An outstanding mental state has also been reported as a key variable to ACL reconstruction success (165).

2.1.4 Functional and subjective testing are useful to determine if an ACL patient is ready to safely return to activities and work

Disruption of the ACL results in varying degrees of functional limitations (42, 59, 166, 167). These are usually associated with the twisting, cutting, jumping or landing movements, which are required in athletic activities (42, 147, 158). In order to accurately evaluate a patient's functional disability and to assess whether a safe return to sports or strenuous work is possible following ACL reconstruction, functional testing has been developed. Among these, the hopping-type tests have been most commonly reported in studies of ACL reconstructed patients. The ability to perform functional tests of the lower extremity within normal values is regarded as an important criterion of recovery and readiness to return to pre-injury activities (58).

A limb symmetry index (LSI), calculated by dividing the value for the involved/uninvolved limb (*100), is often reported as an indicator of the relative deficit in the injured leg (61, 168). The clinical requirement for normal function is considered 85%. This means the involved limb should be functioning at least 85% as well as the uninvolved limb (43). Preliminary data suggest ACL injuries occur more commonly on the 'dominant' leg and that functional and mechanical outcomes are similar between legs pre-injury (169).

Data collected on the normal population demonstrated that limb symmetry of equal to or greater than 90% was normal for males and equal to or greater than 80% was normal for females (170). For the single-leg hop test, it has been reported that the ability to hop 80 – 90% of one's height is considered normal for males, whereas the capacity to hop 70 – 80% of one's height is deemed normal for females (171). Or the ACL patient should have the capacity to perform within 10% of their non-surgical limb (171).

Measurement of functional assessment post-ACL reconstruction

Previous results suggest neither shuttle run tests nor the vertical jump test is recommended for use in detecting lower limb functional limitations (41). In the ACL-deficient population, more than 90% scored in the normal limb symmetry range on the shuttle run tests; patients tended to compensate by running at one-half speed and guarding both legs during turning and cutting movements. A large percentage of normal subjects scored outside of the normal limb symmetry range for the vertical jump test. However, the crossover hop test and the timed hop test expressed the greatest anxiety and fear with most patients (61). Thus, suitable tests for evaluating functional deficits in patients with ACL reconstruction should include twisting and cutting movements, rather than simply straight movements.

A potential drawback of these functional tests is the possibility of reinjury in the test maneuvers for the ACL-deficient patients through the pivoting and jumping activities. The relationship between the safety margin and the effectiveness of the tests warrants further investigation. Additionally, hop testing can only be administered in the late stages of post-operative ACL rehabilitation, and is not appropriate for all patients with ACL deficiency. *Alternative methods to measure function are therefore needed in order to acquire objective information for clinical decision-making regarding progression and rehabilitation protocols (172).*

Number of tests

Although in previous studies the criteria for definition of functional abnormality was different in each report, the percentage of patients who showed abnormal values (sensitivity) was at most 58% (41, 42, 173, 174). For example, 60% of the ACL-deficient knees performed abnormally on at least one out of two tests in the combined test analysis. When only one test was evaluated, the range of abnormality decreased to 42-50%, depending on the test used (42). *Therefore, either at least 2 functional tests should be conducted or other modes to assess function are needed (172).*

Muscular strength

Authors have suggested that the best measure of status in ACL patients is muscular strength. Optimal function following ACL reconstruction is dependent on many factors, of which muscle strength is one of the most important. Thus, a possible explanation for asymmetric function may simply be due to the decrease in quadriceps strength rather than implying functional deficits (167, 172, 175).

Time since surgery

Researchers have proposed that subjects who are further post-surgery may some degenerative changes, which may account for the subjects scoring below normal. Therefore, subjects who are only ½ a year to a 1 ½ post-surgery may have better function than those 10 years post-surgery. In contrast, it appears that as time increases, patients feel better regarding their overall knee functions (61). A trend was noted between overall subjective knee scores and the length of time following the surgery.

Subjective Satisfaction

Researchers and sports medicine professionals have used many subjective surveys to assess the outcomes of treatment (41, 59, 176-183). Two common subjective surveys are the IKDC (International Knee Documentation Committee) and KOOS (Knee and Osteoarthritis Outcome Score) questionnaires, which have been properly validated (184-186). The international standing committee designed the IKDC questionnaire; accordingly it may turn into a publication obligation (184). The IKDC examines level of function and level of symptoms. A mark of 100 is understood to denote no limitation with activities (sports activities and daily living) and a complete lack of symptoms. KOOS measures the subject's attitude about their knee as well as related problems. A mark of 100 is understood to denote a complete lack of symptoms and a score of zero is suggestive of severe symptoms.

KOOS measures the subject's attitude about their knee as well as related problems. A mark of 100 is understood to denote a complete lack of symptoms and a score of zero is suggestive of severe symptoms. The scores are reported by subscale (Pain, Symptoms, Function in Daily Living, Function in Sport and Recreation, Knee Related Quality of Life).

Previous studies have not found that subjective results correlate with strength tests and functional ability in ACL patients (41, 187-189). For instance, despite normal range on the one-legged hop tests, subjective questionnaire results reported that these patients had experienced giving-way episodes with sports activities (41, 42). ACL patients typically perform functional tests under strict and controlled clinical environments, which may be the cause for the lack of relationship often reported between functional scores and subjective measures. The combination of poor subjective scores and normal function may have implications if patients lack confidence, are hesitant and worried or overcompensate when they return to play and activities of daily living. When determining functional and activity limitations, the clinician is advised, first, to interpret results from the hop tests, and, second, to critically analyze patient responses to questions.

2.2. PART II. Theoretical and Technical Overview

2.2.1 Bone's most pertinent asset is strength, which is reliant on mass and material properties as well as bone geometry and architecture.

From the position of evolutionary biology, selection discriminates processes that do not maintain bone's mechanical authenticity by whatever measures are feasible (190). Hence, the objective during growth is to construct a strong skeletal system that will resist mechanical stresses and impede fracture as one ages. Consequently, bone maturity is regulated by the operating demands of bone as a unit (190). Properties such as lightness, flexibility, strength and stiffness compromise contradictory demands of long bones. For instance, bone must be unyielding to guarantee proficient muscle contraction and of course still be accommodating to take in energy to avoid fracture (191).

The mechanical performance of whole bones under physiological loads is reliant on mass and material properties as well as bone geometry and architecture (192). Standardized mechanical tests are performed to define a bone's material properties whereas whole bone structural tests are used to determine a bone's structural properties (192, 193). These tests include directing compression, bending and torsion loads to the bones (193). A load-deformation curve is generated from the data produced, which identifies the structural or extrinsic properties such as whole bone strength, stiffness and energy to failure. Subsequently, these properties require normalization to the size of the bone (cross-sectional area) in order to switch into a stress-strain curve. This curve characterizes the material or intrinsic properties that consist of (194) ultimate stress (strength), elastic modulus and toughness of the bone.

Bone's material properties play a role in overall bone strength and are the traits at the tissue level. The core fundamental biomechanics include strain, stress, yield point and toughness. During a mechanical loading state, the bone will undergo deformation from its initial dimensions. This event is recognized as strain and is defined as the alteration in length over the initial length of the bone (192). Stress is characterized as the intensity of the mechanical load and is calculated as force over the area of bone the load is acting on (195). Tension, compression and shear are the three different types of stress a bone can encounter. The stresses can happen in combination or separately (196).

Stiffness, strength and toughness are taken from the stress-strain graph. The grade of the linear section of the curve symbolizes the material stiffness (modulus of elasticity), which has been named the elastic region. Prior to the yield point, any strain suffered by the bone will be provisional meaning it will go back to its initial shape after the load is eliminated. Following the yield point, permanent deformation will develop (plastic region) until the peak of maximum stress is reached and in the end bone failure is the consequence. The material toughness is the region under the curve and is an essential component to the resistance to fracture (193). Individual traits of secondary osteons within cortical bone such as collage fiber direction, cortical porosity and mineralization have been suggested to be vital to mechanical integrity (191). Overall, bone's elastic properties are impacted only by the mineral phase of the bone. Although, a bone's ultimate strength is concerned with both the content and allocation of bone mineral contained by the matrix (192, 197).

According to Wolff's proposed mathematical construct of guidelines the structure of trabecular bone supplies the necessities for optimal stress transmission due to the combination of proper strength and stiffness in addition to negligible weight (198, 199). These differences contribute to the diversity of mechanical properties and are due to variations in porosity, trabecular thickness and orientation (200, 201).

Bone cross-sectional geometry is multifaceted and differs along the span of the bone. The standard stresses felt by a bone's diaphysis consists of axial compression, bending, shear and torsion or twisting. Defense against these forces is not so much the mass or density, rather the spread and allocation of the cortical bone is more vital (192, 202). The most effective cross-sectional form is when the long bone's mineralized tissue is located as far as possible from the neutral axis of that force. This geometric composition takes full advantage of the strength/lightness ratio, which is best explained through the cross-sectional moment of inertia (I or CSMI). Adding any two perpendicular scores of I equals the polar moment of inertia (J) (203). Additionally, the section modulus (Z) can be calculated from the cross-sectional moment of inertia as I / (D/2) in the bending plane where D represents the cross-section's diameter (203, 204). Of these parameters CSMI, section modulus and polar strength strain index (SSI_p) can be measured by non-invasive means with newer technology (such as pQCT) as discussed in section 2.2.5.

2.2.2 The Mechanostat theory expresses the active regulatory practice whereby bone is adept to react to its mechanical environment

Frost (66) initially proposed that the main stimulus for bone modification was the strain magnitude at the tissue-level. Exceeding an upper limit of strain magnitude would produce the formation of bone while dipping below the lower threshold would cause unnecessary bone to be resorbed. As a result of apposition or resorption, bones adapt to their new, appropriate homeostatic level. However, Frost depicts a threshold range versus one customary strain level where a minimum effective strain exists for remodeling (MESr) as well as modeling (MESm).

This theory has been confirmed in a number of animal studies (205-208). For instance, disuse osteopenia occurred in growing dogs with a casted forelimb via decreased modeling or expansion at the periosteal surface as well as at the endosteal surface intensified remodeling or expansion was demonstrated (207). When the dogs were remobilized both apposition on the periosteal and endosteal surfaces increased and were restored.

Mechanotransduction

Throughout life we constantly encounter mechanical stimuli, which shapes our skeletal system's inherent program to complement the loading requirements we face. In a universal sense, bone adaptation to mechanical stimuli engages feedback loops that work to sustain a balanced or fixed strain level when bone strains are present (209). An increase in stresses on bone such as exercise causes an outcome of bone formation that subsequently decreases the strain on the bone to its previous equilibrium. Conversely, a decrease in bone loads that occurs in situations such as post- ACL injury, or during bed rest or space flight triggers the resorption of bone that once more returns the strain to the programmed level.

It is acknowledged that some type of mechanotransduction is needed to fully execute the cellular steps that are the foundation of bone adaptation (210). Mechanotransduction is the transformation of a mechanical signal into a biochemical signal via mechanical forces directed to a bone. Four phases comprise mechanotransduction in bone, these are: mechanocoupling, biochemical coupling, transmission of signal and the effector cell response (osteoblasts and osteoclasts). The osteocytes have been recognized as cells that play a critical role in adaptations of bone in reaction to two major cues: 1) overuse and 2) disuse.

When a long bone is stressed in compression, and therefore bends at the midshaft of the bone. Due to bone tissue deforming rapidly, fluid pressure gradients are created. These pressure gradients cause extracellular fluid flow shifts, pass from vicinities of compression to vicinities of tension, which causes shear stress on the osteocytes (211). The signaling cascade begins from the mechanoreceptors inside the cell membrane and cytoskeleton. Osteocytes reside in caves named lacunae, which are linked by channels called canaliculi where their dendritic processes are housed. This system of tunnels and enclosures are full with interstitial fluid and are interconnected throughout cortical bone. As a result, intracellular calcium is mobilized and biochemical signals (nitric oxide, prostaglandins) are released from osteoblasts. Prostaglandins have been shown to be anabolic (212), whereas nitric oxide can strongly reduce bone resorption. Within 48 hours of mechanical loading, bone-lining cells separate into synthetic osteoblasts (210, 213), and within 96 hours new bone matrix begins to mineralize (214). In addition, the loading stimulus decreases the speed of programmed osteocyte deaths (215).

Modeling

Bone remodeling and bone modeling are the processes of bone formation and resorption carried out by osteoblasts and osteoclasts. These processes are important for maintaining bone balance. The difference between modeling and remodeling is that modeling refers to independent actions of osteoclasts and osteoblasts on a bone surface. Thus, during modeling, osteoblasts can be forming in one surface or osteoclasts can be resorbing on another surface. These actions of forming or resorbing can be occurring simultaneously or separately. As a result, there are bone changes in size and shape.

Remodeling

As mentioned previously, modeling is an independent action, which is different from remodeling. Therefore, remodeling is a coupled action (BMU) of osteoclasts and osteoblasts. It is a transient operation. This operation consists of three steps: activation, resorption and formation. Bone remodeling is activated when bone lining cells begin to part. As a result osteoclasts start resorbing bone creating a cutting cone within the osteon. Osteoclasts continue to resorb down the bone, while osteoblasts replace bone (~4 months: 3 weeks for resorption, 3 months for formation) (216). Eventually, resorption will still be occurring during formation. Remodeling typically occurs during times of damage repair (target remodeling) or space remodeling. Space remodeling is necessary for removing old bone and replacing it with new and fresh bone. As a result of remodeling there are changes in length and mass.

Activation begins in the company of chemical (hormones) or mechanical signals. Two mechanisms suggested to stimulate these signals are osteocyte-mediated signalling pathways (217) and interstitial fluid flow (218). Bone formation dominates bone resorption throughout our youth; however, during our ageing adulthood the opposite occurs (219). This negative balance may be the consequence of lack of estrogen at menopause (191), immobilization or decreased mechanical loading (220).

Remodeling of cortical bone (intracortical or osteonal remodeling) produces a construction of secondary osteons that are affixed via cement lines with fresh Haversian canals. Cortical bone formation activation rate is greatest during growth (191). A greater quantity of growth hormone and material property variations in the bone matrix during the childhood years are possible reasons for the higher activation frequency. Trabecular remodeling happens in a comparable manner; however, BMUs act on the exterior of trabeculae by excavating and restocking the Howship lacunae or trenches (191). The speed of cortical bone turnover is noticeably slower than that of trabecular bone (~25% per year in adults); however, the pace is known to differ all through the skeleton (191).

Due to the coupled action throughout remodeling, a number of BMUs will be in both the resorption stage and the formation phase. As a result, undermineralization or temporary bone deficits will be found at remodeling sites. (221). This consequence creates a lower elastic modulus (stiffness) and greater strains for a certain load (191). The higher strains may fuel enhanced fatigue damage that sequentially intensifies the activation frequency.

2.2.3 Disuse causes bone adaptations

Decreased muscle strength from reduced mechanical loading or aging decreases the loads on bone, which causes a shift in strains lower than the MESr. The outcome is disuse-mode remodeling that produces a gradual bone loss next to the marrow (222). The customary levels of the mechanostat possibly are changed by hormones and nutrition or other nonmechanical agents (190). In disuse, bone is typically removed from the endosteum, or inner surface of bone. This process rids bone of excess mass, but preserves bone mass distant from the neutral axis, maintaining its bending strength.

Immobilization-induced bone loss is at its fastest during the first 6 weeks. Aguirre et. al. (12) demonstrated osteocyte apoptosis frequency was enhanced in cortical and trabecular bone in tail suspended mice within three days. As a result, bone was resorbed two weeks later. Currently, the mechanism that causes osteocyte apoptosis is not known. It has been proposed that when mechanical loads are absent, signals that usually uphold osteocyte viability are eliminated. Consequently, dying osteocytes motion osteoclasts to resorb bone. Obstruction of nutrient supply and failure to remove waste from the osteocyte have been suggested as explanations for osteocyte apoptosis when there is a lack of loading stimulus. For instance, Knothe Tate et. al. (223, 224) advocated that fluid flow from mechanical loading is required to deliver osteocytes their essential molecules.

Quite a few experiments have alluded to interstitial fluid flow (IFF) as the intermediary for load-stimulated remodeling of the femur (225-229). Two dissimilar methods of action have been suggested. First, load-generated IFF causes bone cells to deform, which leads to stimulation (223, 225-228, 230, 231). Second, oxygen transport from mechanical loading is deprived in disuse models, which causes rapid osteocyte hypoxia (230).

Correlations between periosteal apposition and fluid pressure gradients have been documented when bone deformation was lacking (232, 233). Investigations (234, 235) examining the femur after hindlimb suspension have noticed a decrease in femoral intramedullary pressure. As a result, IFF was diminished, which most likely reduced bone cell deformation; however, sufficient transport of oxygen was maintained. Thus, osteocyte hypoxia may not be an intermediary mechanism for IFF in the femur.

In addition to IFF reduction, previous studies have demonstrated that hind limb suspension (HLS) results in a termination or decrease in bone formation (236-238). After several weeks of femur inactivity it has been shown that there is a decrease in osteocalcin and c-fos gene expression (239). These changes are worth noting, since osteocalcin and c-fos are genes associated with bone formation. After only 1 day, HLS experiments have shown gene expression reduction in the femur. In addition, it was found that after seven days of HLS bone formation rates are reduced and femur cross-sectional area of the mid-diaphysis was decreased (239).

The amount of femur loss from a lack of mechanical loading is highly variable among individuals (240, 241), gender (242, 243), age, and anatomical location (241). Remodeling takes place on the surfaces of bone including trabecular, periosteal, endocortical and osteons (216, 244). Therefore, it makes sense that areas with the most surface area tend to lose more bone. Previous investigations have seen more femur loss in the metaphyses, trabecular bone (245, 246), and females versus the epiphyses, cortical bone, and males, respectively. Although some changes noted in architecture of cancellous bone could reduce bone strength without a significant loss of bone mass. Additionally, the data implies that unloading probably suppresses periosteal growth on the femur. LeBlanc et. al. (247) reported bone mineral density of the neck of the femur and trochanter decreased approximately 0.9 – 1.3% every month from bed rest. In HLS mice versus controls femur mass decreased roughly by 10%, length by about 4%, cortical cross-sectional area around 16%, cortical thickness 25%, CSMI approximately 21% and 2% lower ash was observed after 2 weeks (248).

2.2.4 Rules for bone adaptation to mechanical stimuli

Researchers that have studied both young (249) and mature (250) rats provide proof that bone responds only to dynamic loads. Actually, it seems that static loading suppresses bone adaptations. Dynamic loading comprises three strain variations, which are magnitude, frequency and rate; though, data propose that bone change is more receptive to strain rate (194).

Mosley and Lanyon (251) investigated strain rate on the ulna of young male rats that incurred 14 days of axial compressive loading. The loading protocol consisted of a low, moderate or high strain rate with a steady frequency set to 2 Hz and peak strain magnitudes were comparable for all groups. After the 2 weeks, the best adaptive results were demonstrated by the high rate group (67%) in comparison to the slowest strain rate group. The authors proposed that the higher strain rate possibly inspires the load provoked fluid flow to influence mechanotransduction to a greater degree (251). Specifically, in order to produce effective osteogenic adaptations, ~4,000 – 200,000 microstrain per second will be required (252, 253).

Although strain rate has been shown to be the best, one should not forget the strain magnitude. For instance, among growing rats, greater adaptive responses were demonstrated in those animals subjected to loads of better magnitude (4,000 $\mu\epsilon$) versus normal locomotion loads (1,000 to 2,000 $\mu\epsilon$) (254). During walking, on average, an individual will experience almost a three-fold reduction in strain magnitude versus vigorous activities (~ 2000 $\mu\varepsilon$) (214). According to researchers (221, 255) a microstrain ranging between 200 – 2,000 is necessary if one wants to preserve their bone integrity. Thus, strains less than 200 microstrain, remodeling will commence, and over time net bone loss will be the outcome (221, 255). In opposition, strains higher than 1,500 – 3,000 microstrain generate a positive reaction, which causes an increase in bone mass (255).

In regards to strain frequency, osteogenic results have been demonstrated at 0.5 Hz or higher (256). Efforts by Hsieh and Turner (257) used a protocol of 10 Hz or 1 Hz with rat forelimbs. Rats in the 10 Hz group had a tenfold boost in bone formation compared to the 1 Hz group (257). Additionally other studies have reported positive results when the range was anywhere between 1 – 30 Hz (229, 258).

In 1984, Rubin and Lanyon completed an experiment on the cellular response to loading utilizing the avian ulnar loading method and were able to show that mechanical loading saturates rapidly (250). Ironically, more was not better. Their data suggested that 36 cycles/day, with a magnitude of 2,000 $\mu\varepsilon$ was equal to 1800 cycles/day in an obtaining an osteogenic result. Coincidently, the authors noted that past 36 cycles, there was no enhancement of a bone response.

Often one feels that more is better; however, it appears that increasing the duration of loading is not an important stimulus for bone adaptation. In fact, mechanosensitivity dropped >95% following 20 loading cycles. Although, bone saturates quickly, mechanosensitivity can be brought back to life by recovery periods either within a loading session, or between sets of each bout. For example it was shown in mature rats, separating an everyday loading program into shorter sessions interjected by recovery intervals manufactured greater increases in bone mass, plus geometry and strength versus one solo loading bout (259). It is thought that several bouts separated by recovery time improves the instigation of osteoblasts with fluid flow mechanisms. Possibly long-standing rest time allows the cells to fully return to their "starting positions," whereas multiple shorter sessions with recovery periods does not permit the cells to fully readjust (249). Depending on the attributes of the loading protocol, recovering mechanosensitivity dramatically ranges in time from a few seconds to hours (256). For example, Robling et. al. (249, 260) and Srinivasan et. al. (249, 260) studied different lengths of rest periods in rats (8, 4, 2, 1, 0.5, or 0 h of rest), and reported that the best results were seen when the rest period was four hours or more.

In addition to abnormal impact and loading, regional areas of the same bone receive different strain distributions, which helps bone adaptation. For instance, bending is the key mode of loading on the tibial shaft in the anterior-posterior path, as a result, other regions of the tibia experience tensile and compressive forces (258, 261, 262). Experiments by Lanyon (263) as well as Nikander et. al. (264) demonstrated that the more abnormal the strain distribution is at a site on the bone will cause a greater adaptation of bone mass at that location.

It is also noteworthy to mention here that ground reaction forces (GRF) and muscle forces can elicit bone adaptations. Mechanical loading with high GRF or high impact activities are recognized as important mechanisms for osteogenesis (265-267). As discussed earlier, bone adaptations require magnitudes greater than what one normally experiences in daily living. For instance, high-impact exercise with diverse conditions of movement that require ground reaction forces and rates to be 3.5 - 5 times body mass (267) will be beneficial for the skeleton. Furthermore, it has been established that muscular contractions are the primary loads applied to bone (222, 268-270).

Rubin and Lanyon demonstrated that a strain-related osteogenic stimulus for bone is reliant on many variables such as the number of strains, the rate, the magnitude, and the direction and distribution of the strain(s) (250). Obtaining maximal effectiveness does not require incredibly abnormal or lots of peak strains, instead these studies suggested mechanical loading should occur at high strain rates and the distribution must be uncharacteristic and include variations on the targeted bone(s). Based on the information presented, there are multiple loading strains that alter bone formation and changes. Instinctively, Skerry (252) has offered a new idea for loading strains. He suggests that since it is a combination of strains, and each bone has an individual threshold that really a site-specific customary strain stimulus (SSCSS) is more appropriate.

Adaptive differences between cortical and trabecular bone

Within the human skeleton, woven and lamellar bone are assembled into cortical (or compact) and trabecular (spongy or cancellous) sections (244). Cortical and trabecular bone are different structurally and functionally; however, their material make up is identical (271). Trabecular bone is located at both the proximal and distal ends of long bones and among vertebral bodies, which consists of individual trabeculae and these combine into a three-dimensional lattice object of architecture. The trabecular architecture governs the porousness throughout the areas of trabecular bone (75-95%), presents a substantial surface area where bone turnover or other metabolic activities happen and accommodates bone marrow, which acts in the process of blood cell formation (haematopoiesis).

Contrary to trabecular bone, cortical bone is organized in cylinders, is only 5-10% porous and is located in the shaft of long bones (272). Within cortical bone there is the complex haversian bone, which are settled in osteons with vascular channels while lamellae of bone forms a perimeter surrounding the osteons. These osteons are densely organized and thus, bestows a greater amount of calcification in compact bone (80-90%) than cancellous bone (15-25%). Therefore, one can see the mechanical and protective properties of cortical bone (271).

The bone ends, which house the trabecular bone, have the formation of a broad shape; and thus, functionally acts as a distributor of joint forces. As a result, the load is reduced and is transmitted on to cortical bone from the metaphysis to the diaphysis (273).

It is apparent that adaptations of bone to mechanical loads is complicated, and is affected by a quite a few characteristics among the loading environment. Less is understood about the adaptive response of loading properties in trabecular bone. Authors have proposed that less is known due to the complexity linked with applying and managing loads at the metaphysis or other trabecular sites (274, 275).

The mechanical properties of cortical bone are greatly dependent on strain rate since the material is viscoelastic or time-dependent (191). As a rebound to the overload, osteoblasts add bone on mainly, but not only, the periosteal surface to enhance bone strength. The addition of bone tissue is placed at the location of greatest stress (276); thus decreasing hot spots of stress and greatly reducing the danger of structural failure. The greatest stresses on long bones have been observed on specific areas along the periosteal surfaces. In turn, new bone tissue is placed on the periosteal surface, while the endosteal surface is resorbed. Bone formation on the periosteal surface and resorption on the endosteal surface increases the diameter of the bone and the cross-sectional moment of inertia (CSMI). Even a minor increase on the periosteal surface significantly increases the CSMI since the radius is proportional to the CSMI to the fourth power. Since there is a distance between the neutral axis and most of the bone mass, bone mineral content (BMC) does not need great improvement for bone strength to increase greatly (256, 277, 278).

Joo et al. (279) was able to see bone improvement from treadmill exercise compared to controls. The intervention involved treadmill running for 10 weeks. After the 10 weeks, the authors took measurements from the distal femoral metaphysis in order to examine trabecular aBMD (by DXA) and microarchitecture (with μCT). In comparison to the control rats, the exercise rats showed a significant rise in trabecular aBMD. The increase in trabecular aBMD was attributed to enhanced trabecular thickness, amount and connectivity and a considerable decline in trabecular separation. Though the study did not directly measure trabecular bone strength, the researchers concluded that strength did increase from the structural adaptations based on demonstrated associations between strength and microarchitectural factors (280, 281).

In addition to periosteal apposition, material optimization (stiffer and stronger) can be achieved by trabecular strut alignment. For example, in the proximal femur, trabecular struts have been shown to line up in the path of maximum stresses (198). Similar to the CSMI of cortical bone, alignment of trabecular bone enhances its loading capacity without requiring an increase in bone mass (256, 282, 283). Both cortical CSMI and trabecular alignment demonstrate the skeleton's ability to improve structural efficiency.

2.2.5 Measurement of bone parameters

Bone strength is affected by the quantity tissue within the cross-sectional area and as a general rule, additional bone equals greater strength. Also, the bone's diameter or distribution of mass influences whole bone strength. In order to know the adaptations in bone strength that happen, it is necessary that material as well as architectural characteristics of the bone are measured. This thesis will include pQCT imaging to present a complete assessment of the surgical and non-surgical legs. A discussion of the advantages and disadvantages of using DXA and pQCT are given next.

Dual Energy X-Ray Absorptiometry (DXA)

Presently, the most common method to measure bone mineral health clinically and in research is dual energy x-ray absorptiometry (DXA) (28). The combination of low radiation, noninvasive, brief scanning time and relatively inexpensive are the main strengths of DXA (28). The bone mineral content (BMCg) variable corresponds to the decreased values of photons which go through the X-ray tube and continues to the region of interest. Areal bone mineral density (aBMD, g/cm^2) is calculated from the analysis of the region's projected 2-dimensional area (bone area, cm^2).

The 2-dimensional nature of DXA is an important limitation when measuring a 3-dimensional bony structure (284). Particularly, BMC and aBMD are prone to be undervalued or overvalued since bone size (in 3 dimensions) and geometry adaptations cannot be directly assessed by traditional DXA outcomes (28). To account for the missing dimension, some researchers suggest calculating bone mineral apparent density (BMAD), which is defined as the quantity of BMC over the total bone volume (25). This measure is based on the assumptions that all subjects have similar bone cross-sectional geometry as well as a linear relationship between bone thickness and projectional area (25, 265). This assumption is particularly erroneous when dealing with asymmetric bones such as the tibia, patella, or distal femur (sites relevant to ACL reconstruction).

The failure to differentiate between bone compartments and imprecise associations with soft tissue borders are two other major weaknesses of DXA (28). DXA measurements believe that the structure and allocation of soft tissue at the point of concern all have the same absorption capacities (26). Thus, a heterogeneous distribution of soft tissue about the bone can produce a measurement error in aBMD anywhere from 20 – 50% (27).

Peripheral Quantitative Computed Tomography (pQCT)

Recognizing the limitations of DXA, researchers explored alternate 3-dimensional imaging techniques for assessing bone geometry and strength. Both quantitative computed tomography (QCT) and peripheral QCT have been used in recent years to measure volumetric BMD and bone geometry. Both modalities can distinguish cortical and trabecular bone, but pQCT has better resolution and precision, less radiation, and software that was designed specifically to assess bone geometry and volumetric density of peripheral bones (285-287).

Like DXA, pQCT outcomes correspond to the decreased values of photons which go through the X-ray tube and continues to the region of interest. In contrast, single tomographic slices are used to evaluate bone geometry as well as apparent density of bones within the axial skeleton. These scans are achieved by a rotation method that performs a sequence of transverse tests every 12 degrees (288) until 15 rotations or 180 degrees is accomplished. Each x-ray is absorbed at each angle at the object of concern to generate several absorption reports. These reports are mathematically blended to craft a cross-sectional picture that characterizes the initial object (289). Attenuation coefficients match up with each voxel or single elements within the picture. A customary hydroxyapatite phantom is employed as the comparison value for these coefficients that are converted into volumetric mineral content as well as density (288). The outcome is an assessment of volumetric bone mineral density within the slice. A disadvantage of pQCT is its restricted resolution (higher than DXA but lower than newer high resolution devices); and thus, cannot specifically measure the level of mineralization contained inside the cortex as the vBMD value (apparent density) also incorporates porous spaces (190).

Another issue with pQCT data acquisition is positioning of the reference line. To establish the correct measurement location, the line has to be marked at an anatomical site (289). Before the actual pQCT scan, a scout scan is completed to pinpoint the landmark. Landmark reproducibility is difficult thanks to the dependence on an individuals visual judgment. *Therefore, careful attention must be made to consistent landmarking within studies. In my studies, I personally performed all of the pQCT scans to ensure consistent choices on landmarks.*

An important strength of pQCT over DXA is that pQCT offers estimates of bone strength. Cortical bone distribution at the diaphysis or tibial midshaft impacts torsional as well as bone bending strength (192, 193, 202). To estimate CSMI each pixel's distribution from the reference axis are employed, which has been an accurate indication of bending strength (290, 291). Adding any two perpendicular scores of I equals the polar moment of inertia (J) (203) and is key in concluding stress in torsion (203). The section modulus (Z), another marker of bone bending strength (204) can be calculated from the cross-sectional moment of inertia as I / (D/2) in the bending plane where D represents the cross-section's diameter (203, 204). Additionally, the strength strain index (SSI) integrates section modulus and apparent cortical density (standardized to the physiological density of 1200 mg/cm^3). This SSI has been confirmed against assessments of whole bone strength from animal studies(292). *I therefore use section modulus and polar strength strain index (SSIp) as primary outcomes of bone strength in these studies.*

Muscle

Muscle cross-sectional area (MCSA) can also be measured by pQCT. Two steps employing threshold detection algorithms are required to obtain areas and densities of total and trabecular bone. First, muscle and bone are separated from fat, and second muscle and bone are separated. A third step may be necessary to eliminate the skin if a the voxel size is small. Peripheral QCT derived MCSA has been shown to agree with MCSA derived by spiral CT in adults (R^2 = 0.9) (287), and the literature has reported a 1.93% precision error for adult females (293).

2.2.6 Skeletal muscle fibers can be changed by factors that impact their microenvironment

As noted in section 2.2.7, the strength of bone is dependent on the load placed. Muscle force places the largest load on bone and therefore is an important outcome in my studies. A muscle cell's microenvironment is stimulated by many things such as mechanical loading (exercise) or unloading (inactivity), insufficient energy balance, specific endocrines, exercising in the heat (294), hormonal changes, increase in calcium levels, metabolite accumulation and ischaemia (295, 296). Integrins (proteins linking the cytoskeleton and extracellular matrix) provide receptors for mechanical signals, which causes alterations in the cell's shape (297). This leads to changes in gene expression (297), which is the molecular foundation for anabolic or catabolic adaptations. Alterations in gene expression promote the expression of specific proteins through an intracellular order of signaling events. DNA is transcribed to mRNA, mRNA is translated to protein and protein is degraded to amino acids during this process. If a protein structure is altered, the muscle's phenotype (observable characteristic) will be different. The phenotype is the representation of the underlying genes, which affects the muscle's regulation factors and influences the cellular environment. After ACL reconstruction, the disuse period will stimulate cellular changes, which may be relevant for effective rehabilitative countermeasures and the importance of understanding the muscular adaptations that occur as a result of injury and surgery.

Within a muscle cell the level of protein is decided by the synthesis/degradation ratio. These changes in protein amount and content will modify the muscle's structural and functional properties over time. Additionally, it is important to note that in regards to gene expression, myoplasticity is dependent on the capacity of the muscle fiber's inherent machinery to alter the quality and quantity of protein expression.

Skeletal muscle perspective disuse studies have explored situations of bed rest, cast immobilization and space flight. During bed rest muscle contraction is limited unless deliberate exercise is undertaken. The muscular force required for producing movement, however, is very much diminished once ground reaction forces are removed (298). As a result of inactivity stimuli on the cell's microenvironment, many muscular adaptations are observed such as: less muscle and CSA, fewer metabolic proteins for endurance, reductions of contractile and sarcoplasmic protein (299-302), and quicker atrophy of type I fibers. Biochemical changes are comprised by lower quantities of glycogen, adenosine diphosphate, creatine phosphate, and creatine. Cellular changes involved are sarcomere dissolution, endothelial breakdown (303), significant losses of mitochondria (304, 305) and capillary density declines (306). Within 30 d after the end of bed rest, strength recovers to within 92% of pre-bed rest levels, which provides encouraging evidence that these decrements in muscular force can be overturned within a reasonable amount of time.

Kasper et. al. (307) demonstrated that the commencement of muscle atrophy for acute and ill patients is fast (within 4 hours) and harsh. During the initial two to three weeks, antigravity muscles atrophy larger than non-gravity (307, 308). By the fifth day of bed rest variable but significant increase in urinary nitrogen excretion was noticed (309), which is a marker of increased protein degradation. A negative nitrogen balance is an early signal for dramatic muscle atrophy. Most structural and functional features will continue to change until a stable level is reached. Fortunately, the rate of atrophy appears to decline, which means smaller rates of change occur with long unloading studies.

There does not seem to be a reliable association among neural activity in a muscle and the comparative reduction in muscle mass (298). The losses of contractile strength and power with unloading seem to be consistently greater than the decreases in muscle size and volume (310-313). Studies have provided evidence for a decrease in the electrical efficiency of muscle following relatively brief exposure to muscle unloading. This means after a period of unloading an increase in neural activity is required to elicit the same muscular force output. It is speculated that this altered electrical efficiency may be related to changes in motor unit recruitment as a result of disuse. Support for decreased motorneuron excitability and an impairment of the ability to activate motor units during maximal contractions have been cited as mechanisms for the decrements in muscle strength. Results have shown these decrements in neuromuscular function are completely reversed with 18 wk of strength training (314).

In summary, these data are consistent with clinical evidence presented in section 2.3.2 that muscle size and strength return to pre-surgical levels 12 - 24 months post ACL reconstruction. Section 2.3.2 reviews skeletal muscle data of ACL patients.

2.2.7 Muscle and bone are related.

The main mechanical role of the skeletal system is to supply stiff levers for muscles to contract against as they work against gravitational forces to keep the body upright. (315). The greatest forces on bone are developed from muscle pull (269, 316). Our skeletal system constantly adapts to the stresses encountered in our lives in order to stay within safe limits of bone deformation. Lanyon 1980 has logically proposed that without normal muscle forces, proper long bone development would fail (317). As a result, bone strength is positively influenced by increasing muscle forces (318). It makes sense that the Mechanostat theory hypothesizes that the statistical connection of lean body mass (LBM) and bone mineral content (BMC) signals a direct association (319, 320). Thus, it makes sense that bone recovery is dependent on the degree of healing that the tendons and muscles go through.

Maximal rate of LBM accrual has been demonstrated to occur a few months before the maximal increase in BMC, and the peak rates of change in these two measures were closely correlated (318). It has been suggested that muscle drives and precedes bone development and strength (318). Importantly, Frost (48) suggested that after the fast adaptations of muscle there is a lag before the sluggish responses of bone are seen. Thus, due to the inactivity of the quadriceps, the rate of bone loss will at least be slower; however, so will the recovery. As a result, potentially an avulsion fracture could happen due to the weaker bone being subjected to a stronger muscle pull.

LeBlanc et. al.(321) conducted an experiment to assess the changes in the lower limbs BMC and LBM. The results showed great deficits for both BMC (53%) and LBM (67%). It was suggested that due to the comparable changes in bone and muscle, they must have a close interrelationship, which has been proposed before (322).

In contrast, others have argued that both parameters are independently controlled by other factors, notably genetic determinants (323). Daly et. al. (324) measured total cortical bone, muscle area, polar second moment of area, medullary cross-sectional area and BMC of competitive female tennis players (N = 47, 8 – 17 years). They proposed that other factors, not muscle, are the cause of skeletal adaptations. Their regression equation demonstrated that muscle area accounted for only 12 – 16% of the variance. However, a functional relationship between mechanical forces and bone development is supported by the clinical observation that disease processes interfering with muscle development invariably have a negative effect on bone development (325-327). Other researchers have also found significant correlations between muscle and bone variables (r = 0.77 – 0.87) (221, 328-330).

2.3. PART III. Review of Specific Literature Relevant to Manuscripts

2.3.1 Bone mass and areal density appear to decrease after ACL injury and reconstruction

Researchers have speculated that an ACL rupture together with a reconstruction procedure could be an issue for lower extremity osteoporotic fractures later in life. Customary loading becomes absent after ACL injury and repair due to pain, swelling, instability, and the danger of more musculoskeletal damage. As a result, an individual is not able to preserve their muscle, tendon and bone integrity. An ACL transected limb loading is reduced to ~35% of preoperative levels 2 weeks after surgery and slowly increases to 50 – 60% within 6 – 12 weeks (20, 21). Data has shown that the average nonweight-bearing time after reconstruction is 1.9 $\pm$ 0.6 weeks and partial weight-bearing time is 2.4 $\pm$ 0.8 weeks (22).

Studies of musculoskeletal injuries with subsequent immobilization and disuse of the injured extremity have been seen to result in decreased bone mass and density and it has remained questionable whether full recovery of bone is possible or if the losses are permanent [31-33]. One study (17) demonstrated a 3 – 9% lower BMD at 10-11 years post-injury of the injured knee (femur, patella, tibia) compared to the uninjured knee. Yet these standard BMC and BMD measurements may not be the best representation of bone mechanical strength. Decreases in vBMD, bone geometry, and bone strength after ACL injury and reconstruction are not very well known.

In the limited number of studies that have been performed on animals (7, 8), an agreement has been reached that an ACL transection causes a decrease in BMD at the sites nearest the injury (proximal tibia and distal femur). Although these animal studies do not include surgical reconstructions, which is a very common treatment option in the human population. The human studies performed to date reach a similar consensus that BMD decreases at the sites closest to the injury. In general, the operated leg has decreased areal BMD (as measured by DXA) of 5.1-21% in the distal femur, 6.9-17% in the patella, and 13.9-14.9% in the proximal tibia as compared to the non-operated leg (16, 17, 22, 23, 49, 50). Lacking among these studies are information about volumetric bone density, bone geometry, bone strength and the association with function and subjects' subjective evaluations.

The greatest bone losses nearest the injury appear to be in the trabecular bone (8) and below the subchondral plate (18). A decrease in cancellous BMD and subchondral bone has been suggested to decrease bone strength (6). As a result, the bone strength loss may lead to microfractures affecting the congruence of the joint surface along with subsequent degenerative joint disease (6). Animal studies (8, 60, 331) demonstrate decreases in cancellous bone volume ratio followed by thickening of the subchondral plate. At 54, months increased subchondral thickness, osteophytes and cartilate erosion were noticed. These adaptations signal the natural history of posttraumatic osteoarthritis. However, these studies only used transected ACL's, not reconstructed ACL's.

Researchers (332) have suggested that individuals with osteoarthritis (OA) have poorer bone turnover than those without OA. Quadriceps strength loss, anterior instability, anterior subluxation and meniscal injury have all been suggested as reasons for a higher incidence of OA (9, 38, 333, 334). Almost all patients acquire radiological indicators of OA 15 – 20 years post surgery (36). Researchers have demonstrated that those who undergo a BPTB graft tend to have a higher incidence of OA compared to the hamstring graft (9, 38, 333, 334). This is a clinical concern since BPTB is the most popular graft used for reconstruction. Joint pain from OA may cause gait patterns to change or altered anatomy in an ACL patient. As a result, the distribution of bone loading will be abnormal, which can initiate increased microdamage (335).

Six weeks following surgery, gait characteristics observed became highly different compared to those of the control group. ACL reconstructed subjects produced a highly different tibial translation. No significant differences were found 8 months after reconstruction. The researchers suggested that more time is needed to re-establish pre-injury tibial translation characteristics (37, 336, 337). The measured muscle EMG activity may support the explanation that at least 8 months are required for biomechanical rehabilitation following ACL reconstruction. These authors felt this suggestions was justified since the normal activity of muscles returns 8 months after surgery.

The most important determinants for the development of posttraumatic osteoporosis seem to be the duration of immobilization (17, 23, 49), impaired function of the injured extremity, the surgical intervention, and the patients' own evaluation of knee performance at sports activities (17, 338, 339). Kannus et. al. (17) demonstrated the greatest BMD deficit was found in the patella, which is not a weight-bearing bone. These authors suggested that the disuse of the injured limb is at fault for the decline in BMD. Zerahn et. al. (18) used a region of interest that was located below the subchondral plate as to allow for assessment of BMD at locations that were not directly influenced by the surgical reconstruction of the ACL. Averages and standard deviations of the BMD values were used to transform BMD values from each individual into z-scores in order to overcome differences in BMD related to gender. The injured lateral tibia had a z-score significantly lower than the contralateral leg and comparable controls at 4, 12, and 24 months post-operation.

However, surgical trauma has demonstrated a trend for being the main determinant of posttraumatic osteoporosis. Surgical techniques used for ligament replacement often removes a substantial amount of bone tissue in the knee region (16). First, it has been shown that BMD of the injured leg before surgery neither differed from the contalateral leg nor from that of a group of normal individuals (18). Second, excessive reduction of the BMA in both calcanei appears to be an effect of the surgical intervention and the positive effect of increased activity level was of minor importance despite better function (16). The BMD might decrease in the knee region as a result of the surgical trauma to the knee during the cruciate ligament reconstruction. Thirdly, control limbs of rabbits were significantly different from the sham surgery limbs at 4, 14, and 42 weeks.

Some authors have suggested that the largest decreases occur between 6 and 8 months post-operation (51). Others suggest that the steady state is reached when the bone formation and resorption become balanced, most likely within 6 months after the injury (51, 207). In contrast, Andersson et. al. (23) demonstrated an 18% loss at the proximal tibia within 3 months. Most likely the bone loss is at its fastest during the first few weeks of immobilization followed by a slower loss rate. The literature has reported no signs of bone recovery within 1 year (22, 23). Mean interlimb BMD change was quite large at the 1 year prospective follow-up: Distal femur: -21%; Patella: -17%; Proximal tibia: -14% (22). Studies (16, 18) with a 2 year prospective follow-up have reported lower z-scores and BMA than the contralateral leg and controls at 2 years. Kannus et. al. (17) demonstrated a 3.3 – 9% lower BMD at 10 years post-injury of the injured knee compared to the uninjured knee.

Correct explanations and verification of posttraumatic adaptations of the musculoskeletal system after ACL injury and surgery are needed. A reliable following of the development of recovery, or time line of muscle comparative to bone remains to be answered.

2.3.2 ACL injury and reconstruction causes muscle adaptations.

Deficits in muscle activation and knee extensor torque (340) have been shown to occur post-surgery (341) (342); however, muscle characteristics seem to restore to normal levels with time (9, 45) (9). Conversely, those who choose the BPTB graft tend to have a higher prevalence of significant differences in quadriceps strength between the surgical and non-surgical leg (343). The deficits may be due to either the higher incidence of osteoarthritis (9, 10) or the fact that anti-gravity muscles atrophy larger than non-gravity or both. Flexion strength is within the normal range before and after surgery (46).

Studies have also demonstrated preoperative quadriceps strength deficits in the magnitude of 12-17% due to ACL deficiency (46, 47, 56) The strength deficit in quadriceps muscle strength was much greater after ACL reconstruction. At 6 months post-surgery the surgical leg had 25-36% lower strength than the contralateral limb, which as the highest measured deficit. A clear improvement was noticed between 6 and 12 months. Although recovery of strength was not complete at 12 months post-surgery. The surgical limb was still significantly different to the non-surgical limb (-16-19%). Functional assessment showed identical development. There was a statistically significant relation between an increased quadriceps strength deficit preoperatively and poor early postoperative functional performance. Victor et. al. (45) also showed a significant quadriceps strength deficit 6 months post ACL reconstruction, but reported full recovery at 24 months in a majority of patients. Data suggests that quadriceps strength deficit is related to the ACL injury and is increased by ACL reconstruction. Strategies for overcoming atrophy of the quadriceps muscles may include high intensity eccentric contractions which provide the greatest hypertrophic stimulus (337) and induce a marked neural training effect (336).

ACL patients have demonstrated that they can return their between-legs force production and reactive strength capabilities to a high level of symmetry (344). Reported data demonstrated that ACL-R patients could jump to equivalent heights with both limbs and could produce highly comparable intensities of ground reaction force throughout the jumps (344). This study did not include participants who scored poorly on the IKDC or FPTs, whereas previous researchers did not make a deliberate effort to exclude poorly rehabilitated individuals, their subjects were 27 months postsurgery and had a longer recovery and training stimulus than other studies (47, 345) and all had returned to full activity. Additionally, sensory discrepancies may continue when the ACL is injured and is substituted with a graft source, since a lot of the primary mechanoreceptors and nervous connections are unable to re-establish (346). Over time, it has been proposed that the grafted ACL has the capacity to become reinnervated postreconstruction (347, 348). Additionally, this study was performed in a closed setting. The force sledge apparatus used in this study, can be considered to diminish the stability and coordination difficulties of a jumping task. With a closed environment, the researchers proposed that the force production and reactive strength capabilities can truly be restored post-surgery. Other researchers have (345, 346) suggested that due to postreconstructive deficits in proprioception, force production and reactive strength capabilities are not entirely restored to the limbs of ACL-R individuals (344).

At 1 and 3 months post, data suggests changes in patterns of activation and motor unit recruitment of large, fast contracting muscle fibers (342). In most cases, restoration of voluntary activation was achieved by 3 months after surgery, but muscle weakness persisted. Changes in muscle activation have been suggested as a result of injury or surgery and subsequent alteration in the activity patterns placed on the muscle. Activation failure is characterized as an inability to recruit all motor units to a maximal level usually during a voluntary isometric contraction (340, 349). Most normal healthy subjects have the ability to activate motoneuron pools to a high level (~95%), the level is not consistently 100% (350).

Direct measurements of muscle force can only be determined invasively with force transducers. Most studies examining outcomes after ACL injury and reconstruction use estimates of strength via functional hopping tests, isokinetic dynamometry, and muscle cross-sectional area (MCSA). MCSA is often used as a surrogate of muscle force, but changes in muscle force and strength can be achieved without a change in muscle size due to improvements in neuromuscular recruitment (323).

2.3.3 ACL injury and reconstruction alter the muscle-bone relationship

Mechanical strain associated with physical activity plays a significant role in the regulation of the mechanostat. Physical activity increases muscle forces acting on the skeleton, which in turn should lead to an increase in bone strength. After ACL injury and reconstruction, physical activity and normal loading are not possible.

Rittweger (6) hypothesized that an ACL patient's harvested autologous tendon used for ACL reconstruction causes a weaker original intact tendon. A weaker tendon diminishes the muscle pull on the bone. Therefore, bone loss occurs in the areas of bone that the tendon loads (6). More recently, Reeves et. al. (351) demonstrated that patients with ACL reconstruction are able to recover their patellar tendon stiffness 1 - 10 years after surgery. However, the operated tendon was reported to have inferior material properties. Therefore, the tendon may still be the reason bone deficits are reported after ACL reconstruction.

An experiment by Sievanen et. al. (24), performed a case study on a physically active, healthy 26-year-old female. Initially she was participating in a 46-week lower body strength training intervention. During week 57, the subject tore her anterior cruciate ligament on her left leg in a non-related activity. An ACL reconstruction took place 10 days following the injury. At 14 weeks post-injury bone mineral apparent density (BMAD) weakened by ~25%. Rehabilitation began at 18 months post-injury, which helped attenuate strength losses, but there was no visible gain in BMAD. At 44 weeks post-injury, isometric muscle strength peaked; however, not even 50% of the density damage had been regained. It took a full two years to recover most of the BMAD, which was a full year after strength was back to normal.

Overall, much more exploration is needed to not only to determine the implications of the muscle-bone relationship adaptations following ACL injury and reconstruction, but also understanding what is happening and why those changes occur. The utilization of pQCT in future prospective studies will allow the study of bone geometric changes as well as MCSA adaptations, but will still lack measurements of the tendon.

2.4 Summary

In summary, ACL injuries are common among active individuals and are commonly treated with invasive surgical reconstruction. Although clinical tests currently used to assess functional outcomes post ACL surgery suggest quick recovery, studies suggest athletic performance may be compromised for years in many patients. Therefore, there is a need to explore more sensitive functional measures that can be used in a clinical setting.

In addition to functional outcomes, it is important to understand changes at the bone and muscle level post ACL surgery, which have both theoretical and clinical relevance. Current evidence suggests bone loss occurs post-reconstruction, but it is unclear how bone geometry and mechanical strength are affected and the timing of the muscle-bone loss and recovery are not yet established. Therefore, as noted in the rationale/specific aims section (chapter 1) there is a need to explore changes in bone geometry and strength before and after ACL reconstruction surgery.

The next 3 chapters include manuscripts addressing the specific aims outlined in chapter 1.

3

BONE GEOMETRY AND BONE STRENGTH ARE COMPROMISED IN PATIENTS WITH ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION

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ABSTRACT

The influence of ACL reconstruction on bone geometry and mechanical strength is unclear. Therefore, the purpose of this study was to assess side-to-side differences in bone volumetric density, bone geometry, estimated bone strength and muscle cross-sectional area in patients with a history of ACL reconstruction. We used peripheral quantitative computed tomography (pQCT, Orthometrix XCT 3000) to assess bone geometry (total area, ToA, mm^2), volumetric density (vBMD, mg/mm^3), and an index of compressive bone strength (BSI) at trabecular sites close to the injury (tibia 86%, patella and 4% distal femur). We assessed bone geometry (ToA and cortical area, CoA, mm^2), vBMD, and an index of bone bending strength (strength strain index, SSIp, mm^3) at the cortical sites patella, tibia 66%, and at femur 20%. Muscle cross-sectional area (MCSA) was assessed at 66% tibia and 20% femur sites. We calculated differences in the surgical vs. non-surgical leg in 76 patients (45 females) aged 18-63 years (28.5$\pm$10.6yr) who had undergone a single-side ACL reconstruction in the past 4.5yrs on average and present data as mean difference (95% CI's difference) between limbs. Overall all bone outcomes were lower (0.5-14%) in the surgical leg particularly at sites closest to the injury, specifically trabecular density ((tibia 86% (-4.4%, $p < 0.001$), patella (-5.7%, $p < 0.001$) and femur 4% (-7.7%, $p < 0.001$)). Additionally, at the patella BSI (-12.9%, $p < 0.001$), cortical area (-14.6%, $p < 0.001$), section modulus (-14.2%, $p = 0.001$) and cortical density (-2.7%, $p = 0.011$) were all significantly lower. Though to a lesser extent, femur 20% had significantly lower values ranging from -0.5 to -3.4%. These results support previous DXA studies showing bone loss after suggest ACL reconstruction and also demonstrated strength and geometric changes occur after ACL reconstruction, which may be an important link to a patient's musculoskeletal health.

3.1 Introduction

One of the most prevalent knee injuries in the United States is the rupture of the anterior cruciate ligament (ACL); an estimated 250,000 ACL ruptures occur in the US each year (2). Current guidelines suggest that surgical reconstruction is not a requirement for all individuals who tear their ACL, yet the number of surgical reconstructions performed in the US each year still totals over 100,000 (2, 5, 352). The necessary pre- and post-operative mechanical unloading and disuse results in significant alterations in neuromuscular function and rapid loss of bone and muscle mass (6, 34, 342). These changes can contribute to reduced athletic performance and may increase the risk of osteoporosis and fractures (4, 5, 353), and musculoskeletal disease in later life (i.e. osteoarthritis) (9, 36) as well as negatively affect activities of daily living (4). Therefore, there is a need to identify the short- and long-term effects of ACL reconstruction on bone and muscle strength.

The Mechanostat theory expresses the active regulatory process whereby bone reacts to its mechanical environment by means of increasing bone strength when subjected to larger than normal loads (overload) and rids bones of unnecessary mass when exposed to reduced loads (disuse) (11, 66). In theory, bone mass and strength should return to pre-surgical levels assuming the loading environment has also been re-established. However, previous studies suggest that bone mass does not return to pre-surgical levels even several years after surgery (16, 17, 22), despite an apparent return of muscle strength within 1 – 2 years after surgery (45-47).

Previous studies (17, 22) have assessed bone mineral density (BMD), but lack measurements of bone structure, geometry and strength. These additional measurements provide a more comprehensive representation of the effects of mechanical unloading and disuse than areal BMD alone (24-27). Therefore, the purpose of this cross-sectional study was to explore side-to-side differences in bone strength, geometry and muscle size in patients with previous ACL reconstruction.

3.2 Materials and methods

Subjects

Individuals with ACL injuries who had previous surgical reconstruction were recruited via flyers posted throughout the University campus, a campus wide e-mail, two different sports-related email listings (Marathon & Rugby), a hospital newsletter, and word of mouth. A total of 76 individuals (45 females) participated in the study. Participants ranged in age from 19 to 63 years. Out of the 76 participants 48 had a bone-patella-bone graft (BPTB autograft), 15 had a hamstring tendon autograft, and 13 had a donated patellar tendon from a cadaver (bone-patella-bone allograft) to replace the torn ACL. Time elapsed between injury and surgical reconstruction ranged from 2 weeks to 3.5 years and an average of 4.5 years post surgery. All participants had a single surgical reconstruction of their ACL, were at least six months post surgery, were fracture free (lower extremity) for at least the past five years. Exclusion criteria included bilateral ACL rupture and current pregnancy. Participants completed a health history questionnaire in order to exclude those who had a history of influences on their muscle and bone health such as medications, physical activity, nutrition and menstrual cycle.

Data for each subject was collected during one testing session that lasted approximately 2 hours. All testing was performed at the University of Minnesota Laboratory of Musculoskeletal Health. The protocol was approved by the Institutional Review Board at the University of Minnesota and written informed consent was obtained from each participant prior to beginning the study.

Anthropometry

Body weight was measured by an electronic scale (Tanitia BWB-800, Arlington Heights, IL) to the closest 0.1 kg. Height was measured by a wall-mounted stadiometer (Seca 216, Medizinische Waagen und Messsysteme, Hamburg, Germany) to the nearest 0.1cm.

Clinical and Functional Tests and Questionnaires

Clinical and functional testing were also conducted and can be seen elsewhere (Paper 3). These tests included KT-1000 ligament laxity, single leg hop, crossover triple hop and retro step test. Additionally, the IKDC (International Knee Documentation Committee) and KOOS (Knee and Osteoarthritis Outcome Score) questionnaires were administered.

Peripheral quantitative computed tomography (pQCT)

Bone parameters as well as estimates of bone strength and muscle cross-sectional area (MCSA) of the upper and lower legs were assessed using peripheral quantitative computed tomography (Stratec XCT 3000 bone scanner, Stratec Medizintechnic GmbH, Pforzheim, Germany). One certified technician completed all measurements as well as the analysis of the scans. Quality assurance was executed daily with the cone phantom supplied by the manufacturer.

Participants sat on a chair, with their lower leg extended through the gantry opening, which was 250 mm, on a customized (Bone Diagnostics, Inc.) leg hold and the leg was centered and fixed with Velcro straps around the ankle and mid femur to minimize movement artifacts. A scout scan was conducted before the tomographic scan to delineate the anatomic reference line. At the tibia, the reference line was placed on the articular surfaces of the proximal tibia. At the femur, the reference line was positioned on the distal surface of the medial condyle. At the patella, the reference line was set at 30% of the participant's patella.

Tibia length was quantified from the center of the medial malleolus to the medial joint line of the knee using an anthropometric tape measure. Femur length was measured from the greater trochanter to the lateral joint line of the knee using the same anthropometric tape measure. Two pQCT scans were completed on the tibia and femur at 66% and 86% and 4% and 20%, respectively, of the tibia and femur lengths. The tibia sites were proximal of the medial malleolus, and the femur sites were distal to the greater trochanter. One pQCT scan was taken at 30% of the patella. Identical scans were repeated on the non-operated limb.

The slice thickness for each scan was 2.0mm with a 0.4mm^3 voxel size. In order to distinguish cortical bone scan speed, threshold, contour mode and peel mode was established at 25mm/sec, 710 mg/cm^3, 3 and 4, respectively. At trabecular sites a threshold range, filter, contour mode and peel mode were set to 141 and 650 mg/cm^3, 1, 1 and 4, respectively. Cortical and trabecular bone results comprised measurements of the mass and tissue density (BMC, mg and vBMD, mg/cm^3) (Tables 3 and 4). To estimate compressive bone strength (BSI) was calculated: BSI = ToA*ToD^2. Muscle cross-sectional area (MCSA) were concluded from the slices taken at the 66% tibia and 20% femur for both lower limbs.

3.3 Data Analysis

Statistical analyses were performed with SPSS software Windows Version 13.0 (SPSS Inc., Chicago, IL). All data were first cleaned and checked for outliers or missing values. We report percent difference between the healthy and surgical legs (((healthy leg – surgical leg)/ healthy leg)) x 100) to describe side-to-side differences. We used 95% confidence intervals to determine significance.

3.4 Results

Descriptive characteristics for all participants are shown in Table 3-1. During the cleaning and checking of data, 2 outliers were observed and removed 1 from the female group and 1 for the male group for time between injury and surgery. These same individuals were also removed from the mature group mean for time between injury and surgery.

Table 3-1. Descriptive characteristics of all ACL participants (mean ± SD).

	Overall (n = 76)	**Male** (n = 31)	**Female** (n = 45)
Age	29.6 (11.2)	34.0 (10.2)	25.4 (9.5)
Age at surgery	25.1 (11.1)	30.0 (9.9)	20.3 (8.7)
Weight (kg)	76.1 (16.6)	83.0 (11.6)	71.3 (18.0)
Height (cm)	170.6 (15.2)	179.3 (6.7)	164.5 (16.6)
Time since surgery (mos.)	54.6 (39.1)	48.3 (33.6)	61.2 (42.2)
Time b/t injury & surgery (mos.)	5.2 (10.3)	5.1 (8.4)	5.3 (11.4)

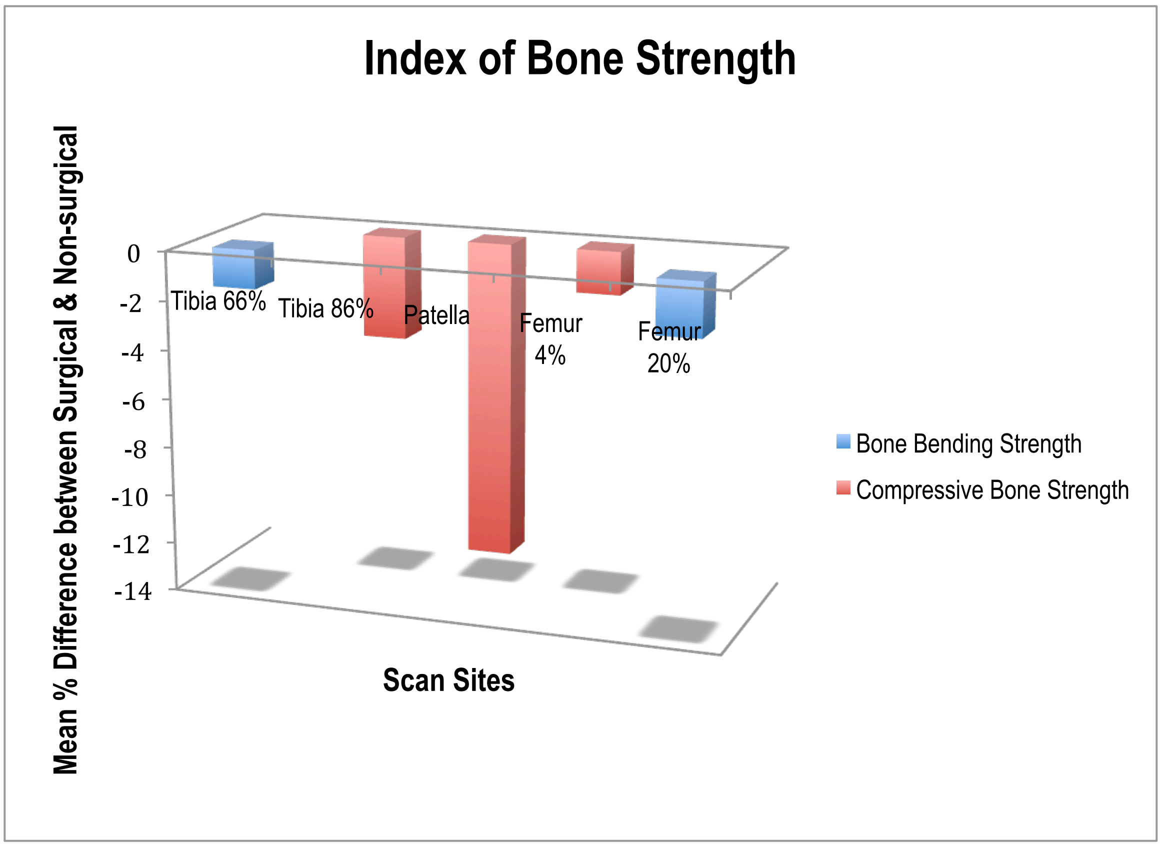
Bone outcomes: mean percent difference (Figure 3-1)

Overall all bone outcomes were lower (0.5-14%) in the surgical leg particularly at sites closest to the injury. Trabecular density was significantly lower at tibia 86% (-4.4%, $p < 0.001$), patella (-5.7%, $p < 0.001$) and femur 4% (-7.7%, $p < 0.001$) and all had similar or greater trabecular area compared to their contralateral leg.

Compressive strength (BSI) was significantly lower at the patella (-12.9%, p <0.001) due largely to a significantly lower total area (-13.3%, $p < 0.001$). Like total area, cortical area (-14.6%, $p < 0.001$), section modulus (-14.2%, $p = 0.001$) and cortical density (-2.7%, $p = 0.011$) were all significantly lower at the patella. Trabecular area was significantly greater at the patella (14.6%, *p* < 0.001) most likely due to a significantly lower trabecular density (-5.7%, p = 0.001).

Although significantly lower, muscle CSA was similar between sides at both the tibia (-1.5%, p = 0.030) and femur (-0.5%, p = 0.001). However, femur 20% had significantly lower cortical area (-3.4%, p < 0.001), section modulus (-2.5%, p < 0.001) and cortical density (-0.5%, p = 0.005).

Figure 3-1. Index of bone strength as % difference between the surgical and non-surgical leg



3.5 Discussion

In this cross-sectional study, we explored side-to-side differences in bone and muscle strength in patients with a history of ACL reconstruction. We found that in general, bone outcomes were lower in the surgical leg particularly at sites closest to the injury, despite the return of muscle mass. The lower scores of the surgical leg are in agreement with prior ACL and bone studies (16, 18, 22, 23), which reported deficits in bone mineral density at sites closest to the injury. These studies used either DXA (17, 22) or dual-energy photon absorptiometry (DPA) (16, 18), whereas in the present study, pQCT was utilized.

Our results did demonstrate deficits in trabecular vBMD. A decrease in trabecular vBMD and subchondral bone at the distal femur has been suggested to decrease bone strength (6). However, trabecular area seems to remain comparable to the contralateral leg or adapts to be significantly greater. Previous studies have shown faster bone loss from trabecular bone compared to cortical bone (16, 354).

Our data revealed significant losses at the patella. Jaworski et. al. (13) reported that after a disuse period the greatest bone loss compared to the initial volume occurred in the smaller bones of dogs. However, the surgical procedure may also be to blame for the drastic bone changes in the patella. Away from the injury, femur 20% showed significantly lower cortical area, section modulus and cortical density. A larger endocortical surface, like femur 20%, has been demonstrated to be particularly responsive to bone loss during disuse (355). If the bone reacts to surgical intervention by resorbing more bone than is laid down, but the remodeling is done in such a fashion as to retain the strength of the bone, an increase in fracture risk will not be seen, but the increase in the risk for osteoarthritis may still be present. Although a slight deficit in strength strain index was demonstrated at femur 20%, suggesting ACL reconstruction impacts bone strength.

The return of muscle mass after surgery is also in agreement with previous work (45, 47), which demonstrated the return of muscle strength to non-injured leg levels over time. The average time since surgery for our participants was 53 months. Several studies have reported preoperative strength deficits of 12 – 17% in the quadriceps due to ACL deficiency (9, 46, 47, 56). After ACL surgery quadriceps muscle strength demonstrated much larger deficits, with the healthy leg having 25-36% more strength than the injured side 6 months post-surgery. Even measurements at 1 year showed lack of recovery with significant strength side-to-side differences of 16 – 19%. Victor et. al. (45) also reported a significant quadriceps strength deficit 6 months after surgery, but full recovery was observed in the majority of patients at 24 months. The concern lies in the fact that many athletes return to play less than 1-year after surgery when strength deficits are still apparent. Our data suggest that muscle size returns. Notably, we used muscle cross-sectional area as a surrogate for muscle strength (329, 356). The previous studies directly measured muscle strength with isokinetic dynamometry. Despite this methodological difference, as a result of positive stimuli, many muscular adaptations are observed, one of which is greater cross-sectional area (357-359). Since our participants on average were 53 months post surgery, all patients have had the ability to load their leg muscles. MCSA has been shown to be related to parameters of conduction velocity and median frequency of a muscle contraction (360). Additionally, muscle atrophy (volume or CSA) (360) has been reported as an adequate and reliable mechanism for the evaluation of muscle recovery and function after an ACL surgery (175).

In the current study, although muscle size in the injured leg appeared to recover, bone did not, which contradicts the Mechanostat Theory. The largest forces within musculoskeletal system arise from muscle pull (269, 361). However, tendons are responsible for transmitting these muscular forces. Previously, Rittweger et. al. (6) proposed that the tendon could be the reason bone deficits are seen in ACL patients post-surgery. Rittweger hypothesized that tissue harvesting causes weakening of the formerly intact tendon, which, in turn, leads to reduced muscle pull and subsequent bone loss in those parts of the bone that are loaded by the tendon (6). Studies using both surgical and non-surgical ACL patients have demonstrated that the surgical group lost significantly more BMD than the non-surgical group (22, 23). More recently, Reeves et. al. (351) demonstrated that patients with ACL reconstruction are able to recover their patellar tendon stiffness 1 - 10 years after surgery. However, the operated tendon was reported to have inferior material properties. Therefore, the tendon may still be the reason bone deficits are reported after ACL reconstruction.

Animal studies show that scar tissue formation does take place for several months after and ACL operation. One study on sheep showed that the operated patellar tendon recovered its normal stiffness within 12 months after the operation(362); however, another 2 studies, one on dogs and the other on goats, yielded a different result: the operated dog patellar tendon had a reduced stiffness by 33% compared to the control site 6 months after the operation (363), while the operated goat patellar tendon had a reduced stiffness by 27% compared to the control site even 21 months after the operation (364). The harvesting of a tendon could explain the results we found, but there is not enough consistent evidence. Future prospective longitudinal studies will need to test this hypothesis.

In the current study, we noticed that males and older participants appeared to have lower bone strength in the surgical leg at sites nearest to the injury compared to females and younger participants, respectively. Our results are in agreement with previous bone fracture studies. Nilsson (365) demonstrated that after a fracture of the tibia, bone loss in the femur was generally more pronounced in male patients than female patients. Previous studies in children after a fracture of the tibia have demonstrated full recovery or even exceeded the contralateral limb (366, 367). Age and gender trends may be worth exploring in future prospective longitudinal ACL studies.

3.6 Conclusion

Overall are results demonstrated bone outcomes were lower in the surgical leg particularly at sites closest to the injury. Almost all outcomes were shown to be significantly lower at the patella. Though more minor compared to nearest the injury, femur 20% did display significantly lower values up to -3.4%. These results illustrated that strength and geometric adaptations happen after ACL reconstruction. More evidence is needed to determine if these strength and geometric changes are an important link to a patient's musculoskeletal health.

4

BONE GEOMETRY AND BONE STRENGTH CHANGES IN PATIENTS WITH ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION: PROSPECTIVE OBSERVATIONS A PILOT STUDY

Myhre SL, Gaddie T, Rittweger J, Hughes JM, Wetzsteon RJ, Stovitz SD, Larson CM, Petit MA, Giveans M

Anticipated Submission, 2010

ABSTRACT

The purpose of this pilot study was to explore bone strength, geometry and muscle before surgery, 4 - 6 weeks post, 4 months post, 6 months post and 9 months after ACL reconstruction. We used peripheral quantitative computed tomography (pQCT, Orthometrix XCT 3000) to assess bone geometry (ToA, mm^2), volumetric density (vBMD, mg/mm^3), and an index of compressive bone strength (BSI) at trabecular sites close to the injury (tibia 86%, patella and 4% distal femur). We assessed bone geometry (ToA and cortical area, CoA, mm^2), vBMD, and an index of bone bending strength (strength strain index, SSIp, mm^3) at the patella, 66% of the tibia, and at 20% of the femur. Muscle cross-sectional area (MCSA) was assessed at 66% tibia and 20% femur sites. We calculated differences of their surgical leg from the baseline measures vs. 4 and 9 month measures in 6 patients (1 male) aged years (34.7 $\pm$ 13.7). The greatest percent deficits were found at sites closest to the injury (tibia 86%, patella and femur 4%). Compressive strength (BSI) deficits were evident at tibia 86%, patella and femur 4% ranging between -3.1% to -29.7% as well as trabecular density at tibia 86% (-0.7% to -12.0%), patella (-2.2% to -12.0%) and femur 4% (-5.3% to -11.3%). Still other outcome deficits were demonstrated at the patella, including section modulus (-11.5% to -27.7%), cortical area (-4.0% to -18.4%) and total area (-11.8 to -29.1%). In comparison to baseline, by 9 months post sites away from the injury, tibia 66% and femur 20% were comparable to baseline measures. Compressive strength (BSI) at tibia 86%, patella and femur 4% (range -14.6% to -20.9%) and cortical area (-14.2%) and section modulus (-19.5%) at the patella still showed noticeable deficits at 9 months compared to baseline. This pilot study demonstrates the need for prospective longitudinal studies with more subjects and longer follow up periods to explore if ACL injury and reconstruction have significant implications for optimal musculoskeletal health.

4.1 Introduction

Anterior cruciate ligament (ACL) tears are a fairly common injury among professional and recreational athletes (1) as well as nonathletes. Customary loading becomes absent after ACL injury and repair due to pain, swelling, instability, and the danger of more musculoskeletal damage. An ACL transected limb loading is reduced to ~35% of preoperative levels 2 weeks after surgery and slowly increases to 50 – 60% within 6 – 12 weeks (20, 21). Data has shown that the average nonweight-bearing time after reconstruction is 1.9 $\pm$ 0.6 weeks and partial weight-bearing time is 2.4 $\pm$ 0.8 weeks (22). According to the well-established mechanostat theory, changes in mechanical loading is the primary factor to which bone adapts its strength. Loading and disuse studies in animals support the theory that bone strength adapts appropriately to changing mechanical loads. In the human literature there are few studies exploring changes in bone strength and geometry as a consequence of ACL injury. Prior studies (17, 22, 23) have focused on bone mass and areal density as primary outcomes, which makes data less convincing. Bone may alter it's strength by changing not only mass and density, but also geometry and structure. The ability to measure bone volumetric density, bone geometry and estimates of bone strength are now possible due to the advancement in technology.

Exploring bone volumetric density, geometry and estimates of bone strength in ACL reconstructed patients from both legs prospectively will provide a reliable following of the development of recovery, or time line of muscle comparative to bone. A study like this will correctly explain and verify posttraumatic adaptations of the musculoskeletal system after ACL injury and surgery.

Therefore, the purpose of this study was to explore bone strength, geometry and muscle before surgery, 4 - 6 weeks post, 4 months post, 6 months post and 9 months after ACL reconstruction using peripheral quantitative computed tomography (pQCT).

4.2 Materials and methods

Subjects

Individuals who had torn their ACL and were scheduled to have surgery were recruited via a staff member at a local sports medicine clinic. The study included 6 subjects, 5 females and 1 male who ranged in age from 17 to 53 years. Out of the 6 participants 2 had a bone-patella-bone graft (BPTB autograft) and 4 had a donated patellar tendon from a cadaver (bone-patella-bone allograft) to replace the torn ACL. Exclusion criteria included pregnancy due to the pQCT scans. Out of the 6 participants 1 completed scans up to 9 months post-surgery, 4 completed the scans up to 6 months and the other 1 up to 4 months. The protocol was approved by the Institutional Review Board at the University of Minnesota.

Data for each subject was collected before surgery and 1, 4, 6 and 9 months after surgery, which lasted approximately 1 hour. All testing was performed at the University of Minnesota Laboratory of Musculoskeletal Health. Prior to participation, informed consent was obtained from each subject.

Peripheral quantitative computed tomography (pQCT)

Bone parameters as well as estimates of bone strength and muscle cross-sectional area (MCSA) of the upper and lower legs were assessed using peripheral quantitative computed tomography (Stratec XCT 3000 bone scanner, Stratec Medizintechnic GmbH, Pforzheim, Germany). One certified technician completed all measurements as well as the analysis of the scans. Quality assurance was executed daily with the cone phantom supplied by the manufacturer.

Participants sat on a chair, with their lower leg extended through the gantry opening, which was 250 mm, on a customized (Bone Diagnostics, Inc.) leg hold and the leg was centered and fixed with Velcro straps around the ankle and mid femur to minimize movement artifacts. A scout scan was conducted before the tomographic scan to delineate the anatomic reference line. At the tibia, the reference line was placed on the articular surfaces of the proximal tibia. At the femur, the reference line was positioned on the distal surface of the medial condyle. At the patella, the reference line was set at 30% of the participant's patella.

Tibia length was quantified from the center of the medial malleolus to the medial joint line of the knee using an anthropometric tape measure. Femur length was measured from the greater trochanter to the lateral joint line of the knee using the same anthropometric tape measure. Two pQCT scans were completed on the tibia and femur at 66% and 86% and 4% and 20%, respectively, of the tibia and femur lengths. The tibia sites were proximal of the medial malleolus, and the femur sites were distal to the greater trochanter. One pQCT scan was taken at 30% of the patella. Identical scans were repeated on the non-operated limb.

The slice thickness for each scan was 2.0mm with a $0.4mm^3$ voxel size. In order to distinguish cortical bone scan speed, threshold, contour mode and peel mode was established at 25mm/sec, 710 mg/cm^3, 3 and 4, respectively. At trabecular sites a threshold range, filter, contour mode and peel mode were set to 141 and 650 mg/cm^3, 1, 1 and 4, respectively. Cortical and trabecular bone results comprised measurements of the mass and tissue density (BMC, mg and vBMD, mg/cm3) (Tables 3 and 4). To estimate compressive bone strength (BSI) was calculated: $BSI = ToA*ToD^2$. Muscle cross-sectional area (MCSA) were concluded from the slices taken at the 66% tibia and 20% femur for both lower limbs.

4.3 Data Analysis

All data were first cleaned and checked for outliers or missing values. We report percent difference of participant's surgical leg between the baseline measures and at 4 and 9 months (((baseline measure – surgical leg)/ baseline measure)) x 100) to describe changes over time.

4.4 Results and Trends

Data were collected on a total of 5 women and 1 man who ranged in age from 17 to 53 years of age. The heights ranged between 156.2 to 181.6 centimeters and weight ranged from 51.6 to 80.5 kilograms. Participant descriptive characteristics are shown in Table 4-1.

Table 4-1. Descriptive characteristics of all ACL participants (mean ± SD).

	Overall (n = 7)	**Male** (n = 1)	**Female** (n = 6)
Age	34.7 (13.7)	26.0	36.4 (14.6)
Weight (kg)	62.9 (11.2)	80.5	59.4 (8.0)
Height (cm)	165.4 (9.1)	181.6	162.2 (5.1)

Bone outcomes "trends": mean percent difference- baseline to 4 months

Overall all bone outcomes with the greatest percent differences were at sites closest to the injury. Compressive strength (BSI) mean percent difference were noticeable at tibia 86%, patella and femur 4% ranging between -3.1% to -29.7% (Figures 4-1 and 4-2). In addition, trabecular density at tibia 86% (-0.7% to -12.0%), patella (-2.2% to -12.0%) and femur 4% (-5.3% to -11.3%) had fairly large percent differences from baseline. Section modulus (-11.5% to -27.7%), cortical area (-4.0% to -18.4%) and total area (-11.8 to -29.1%) also demonstrated some large percent deficits from baseline at the patella. Away from the injury, femur 20% demonstrated deficits in cortical area (-1.7% to -9.6%) and section modulus (-1.6% to -10.5%).

Bone outcomes "trends": mean percent difference- baseline to 9 months

Similar to baseline and 4 months, bone outcomes with the greatest percent differences were at tibia 86%, patella and femur 4%. Away from the injury, tibia 66% and femur 20% were comparable to baseline measures. Compressive strength (BSI) still demonstrated noticeable deficits at tibia 86%, patella and femur 4% ranging between -14.6% to -20.9%. Cortical area (-

14.2%) and section modulus (-19.5%) at the patella appeared to have quite a deficit at 9 months compared to baseline.

Figure 4-1. BSI % difference change at femur 4% from pre-surgery to 4 months post-surgery for each participant

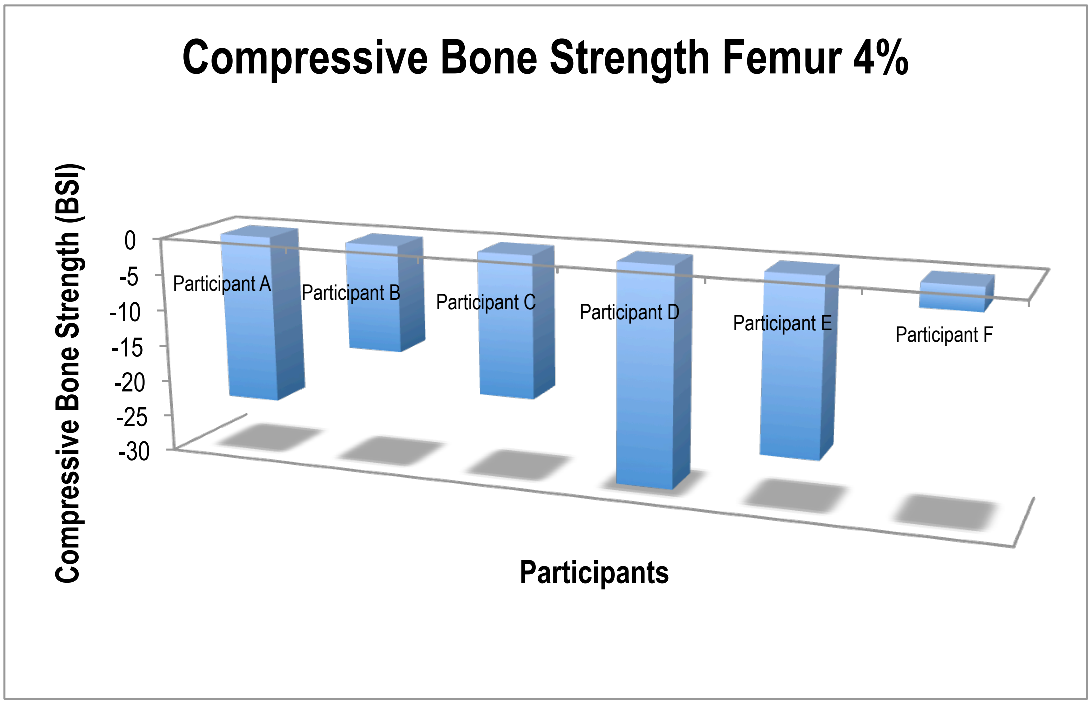
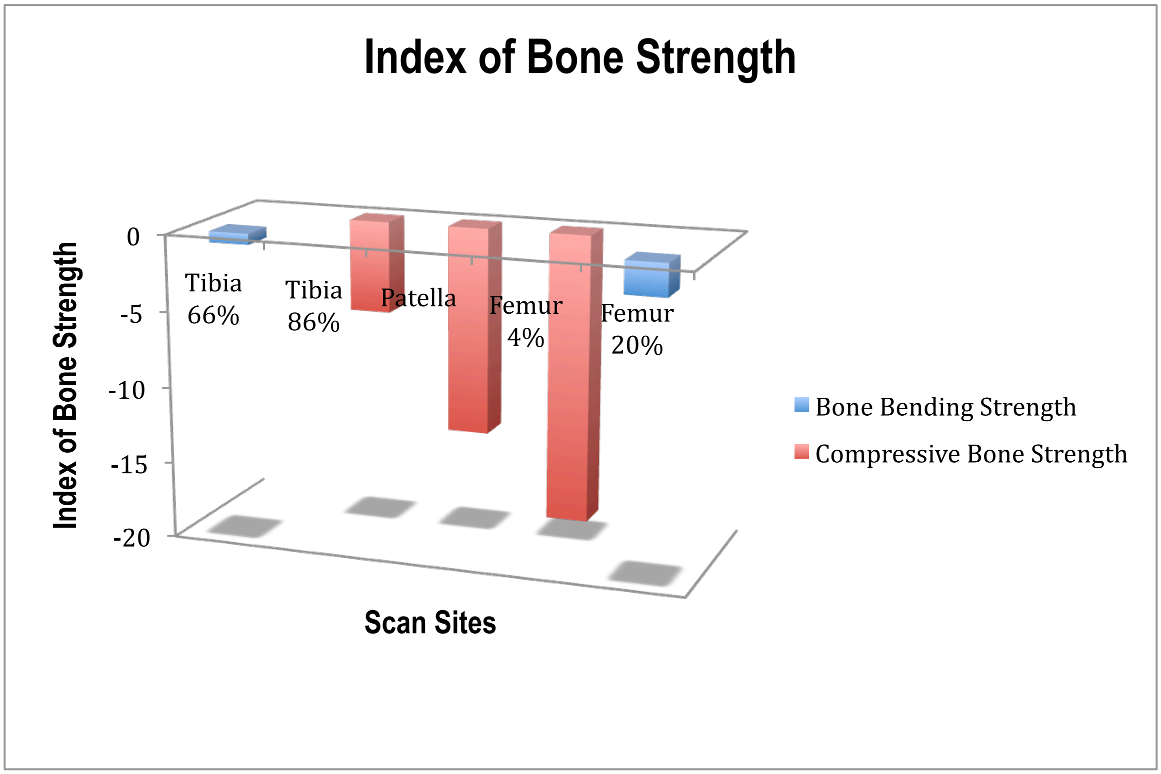


Figure 4-2. Mean % difference for index of bone strength at each scan site from pre-surgery to 4 months post-surgery



4.5 Discussion

The present study aimed to explore bone strength, geometry and muscle before surgery, 4 - 6 weeks post, 4 months post, 6 months post and 9 months after ACL reconstruction. Overall all bone outcome trends were shown to have the largest percent differences at sites closest to the injury, which were trabecular sites. Prior studies have demonstrated quicker bone loss from trabecular bone compared to cortical bone (16, 354). Compressive strength (BSI) mean percent difference were noticeable at tibia 86%, patella and femur. A decrease in trabecular vBMD and subchondral bone at the distal femur has been suggested to decrease bone strength (6). Future prospective longitudinal studies will be needed to determine if ACL injury and reconstruction posttraumatic osteopenia can or cannot recover and if the risk of fractures in later life may be unavoidable despite proper prevention and rehabilitation efforts (16, 19, 34).

Trabecular density at tibia 86%, patella and femur 4% had fairly large percent differences from baseline. Section modulus, cortical area and total area also demonstrated some large percent deficits from baseline at the patella. Jaworski et. al. (13) discovered that the largest bone loss compared to the original volume occurred in the smaller bones of dogs after a disuse period. Possibly why we saw so many deficits at the patella. Subsequent studies will need to explore the implications of deficits at the patella and around the injury due to ACL reconstruction.

Away from the injury, femur 20% demonstrated deficits in cortical area and section modulus. Mechanical loading effects on bone geometry have been shown to be stronger in portions of cortical bone (264). Additionally, femur 20% is a site with more endocortical surface compared to other sites. A larger endocortical surface is especially susceptible to bone losses due to disuse (355). Our results appear to be similar to other disuse model reported results (13, 14, 354), which implies bone and muscle data from other disuse model studies may be applicable to ACL patients and their musculoskeletal health. Furthermore, if the bone responds to ACL reconstruction by resorbing more bone than is laid down, but the remodeling is done in such a manner as to preserve the strength of the bone, an inflation in fracture risk will not be observed, but the increase in the risk for osteoarthritis may still be demonstrated. Although a deficit in strength strain index trend was shown at femur 20%, which implies bone strength was influenced by ACL surgery and injury.

Away from the injury, tibia 66% and femur 20% were comparable to baseline measures at 9 months. Since MCSA was comparable to baseline measures at 9 months post, it suggests that muscle has recovered. Prior studies have demonstrated a clear improvement in muscular strength between 6 and 12 months post surgery (37, 46). Considering muscle drives and precedes bone development as well as positively influences bone strength, may be the reason for tibia 66% and femur 20% demonstrating outcomes relative to baseline. In contrast to prior results (16, 17, 19, 22), our pQCT study may suggest that bone can be overturned with increased mechanical loading and activity.

Similar to baseline and 4 months, at 9 months bone outcomes with the greatest percent differences were at tibia 86%, patella and femur 4%. Compressive strength (BSI) still demonstrated noticeable deficits at tibia 86%, patella and femur. Cortical area and section modulus at the patella appeared to have quite a deficit at 9 months compared to baseline. After injury, a steady state from disuse will only occur when bone formation and resorption are equivalent, typically within 6 months (17, 19). The differential time course from muscle adaptation, bone adaptation can take approximately 3 - 4 months for a conventional remodeling cycle (55). Additionally, the latest steady state may not be mature and completed for measurement for 6 - 8 months (55). Thus, studies with longer follow-up periods are necessary to elucidate the muscle and bone recovery after ACL injury and reconstruction.

4.6 Conclusion

Our pilot results demonstrated trends that overall bone outcomes with the greatest percent differences were at sites closest to the injury. Compressive strength (BSI) deficits were very noticeable at tibia 86%, patella and femur 4% at 4 and 9 months compared to baseline measures. Out of all the sites the patella showed deficits in most of the outcome measures. In general, away from the injury, revealed comparable values to the baseline values. Prospective longitudinal studies with more subjects and longer follow up periods are required to determine if ACL injury and reconstruction have significant implications for optimal musculoskeletal health.

5

OBSERVING FUNCTIONAL ABILITY AND SUBJECTIVE SATISFACTION UP TO 18 YEARS POST ACL RECONSTRUCTION

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ABSTRACT

The purpose of this study was to 1) observe functional ability in patients with a history of anterior cruciate ligament reconstruction and 2) explore the sensitivity of a novel assessment of functional strength. A total of 63 participants (25 males, 38 females) who had a single surgical reconstruction in the past 1-18 years (mean 4.5 yrs) were evaluated. Clinical and functional assessments including KT-1000 ligament laxity, single leg hop, crossover triple hop and retro step test were conducted as well as the IKDC (International Knee Documentation Committee) and KOOS (Knee and Osteoarthritis Outcome Score) questionnaires. Limb symmetry indices (LSI) were calculated ([(surgical/non-surgical)*100] to express function of the surgical limb relative to the healthy limb. On the single leg hop, the single leg crossover hop, and the retro step, 11%, 18%, and 30% of the participants, respectively had LSI's below 85% for each test. Twenty of the subjects had > 3 mm of excursion on the KT-1000 ligament laxity assessment. The KOOS questionnaire showed inferior scores for the symptoms subscale (range, 39.0 – 79.0), knee related quality of life subscale (range, 31.0 – 100), and function in sport and recreation subscale (range, 45 – 100). There were no clear associations with functional outcome and age of surgery, gender, time since surgery or graft type. We showed that reduced functional ability and poor questionnaire scores are still apparent in patients 1-18 years post-ACL reconstruction. Of the functional assessments we conducted, the retro step test showed the highest percentage of participants with decreased functional outcome. This assessment may be a useful addition to the standard set of clinical assessments.

5.1 Introduction

In the discipline of orthopedics and sports medicine few injuries have spawned as much interest as anterior cruciate ligament (ACL) injuries (1). An ACL injury is associated with many consequences such as bone and muscle loss, reduced tendon stiffness as well as functional and neuromuscular deficits (47, 59, 170, 341, 368, 369). These hindrances cause extensive recovery time and the unfortunate likelihood that 100% performance and function will not transpire for ACL patients (4, 5, 353). An ACL injury occurs mainly with athletes but happens to non-athletes as well. An estimated 250,000 ACL ruptures occur in the United States each year (2, 3) and of those, an estimated 100,000 reconstructions are completed each year (5, 352, 370).

To fully capture the ability to return to play as well as activities of daily living, muscle strength and clinical and functional outcomes are commonly measured on ACL patients. The ability to perform functional tests of the lower extremity within normal values is regarded as an important criterion (58). The results of functional tests are based on contralateral limb scores or LSI. The literature generally recommends attainment of 85% or greater of the contralateral score as an acceptable measure of function or return to play. This means the involved limb should be functioning at least 85% as well as the uninvolved limb (41). Researchers have proposed that subjects who are further post-surgery may have some degenerative changes such as periarticular osteopenia, cartilage degradation, joint space narrowing and thickening of the subchondral plate (7, 34, 60), which may account for participants scoring below normal on functional tests. Therefore, subjects who are only ½ a year to a 1 ½ post-surgery may have better function than those 10 years post-surgery. However, subjectively it appears that as time increases, patients feel better regarding their overall knee function (61).

Despite the vast clinical and research interest in ACL injury and reconstruction, there are few published studies aimed at long-term functional ability. The few studies (9, 38, 39) that range from 6 - 10 years post surgery and 24 years post (40), focus on comparing functional outcomes between different donor sites. A limitation of these studies is that they assess function primarily using questionnaires and do not directly assess function or use only the single leg hop test (9, 38-40).

Overall, there is a lack of long-term data with direct assessment of functional outcomes in patients with a history of ACL reconstruction. Therefore, the purpose of this study was 1) to describe both subjective and clinical functional outcomes in patients with a history of ACL reconstruction; and 2) to identify clinically useful tests of function in this population.

5.2 Materials and methods

Subjects

We recruited 63 participants (38 females and 25 males, 19-63 years) who had a previous reconstruction of their ACL. 43 subjects had a bone-patella-bone graft (BPTB autograft), 9 had a hamstring tendon autograft, and 11 used a donated patellar tendon from a cadaver (bone-patella-bone allograft). All subjects had a single surgical reconstruction of their ACL. Exclusion criteria included bilateral ACL rupture and pregnancy at the time of study. Subjects were recruited via flyers posted throughout the University campus, a campus wide e-mail, two different email listings (Twin Cities Marathon & MN Rugby), a hospital newsletter, and word of mouth.

Procedures

Data for each subject was collected during one testing session that lasted approximately 2 hours, which included peripheral quantitative computed tomography scans for a concurrent study. All testing was performed in the University of Minnesota Laboratory of Musculoskeletal Health. Prior to participation, informed consent was obtained from each subject in compliance with the University of Minnesota Institutional Review Board (IRB). Experimental measures were assessed in the following order for all participants: 1) ligament laxity, 2) single leg hop, 3) single leg crossover triple hop, 4) the retro step test, and 5) questionnaires. All measurements were conducted by one licensed physical therapist on the uninvolved leg followed by the involved limb.

KT-1000 Ligament Laxity

A KT-1000 arthrometer (MedMetrics, San Diego, CA, USA) was used to assess anterior translation. A side-to-side difference that exceeds more than 3 mm between the noninjured and injured limb indicates an unstable knee while a difference of 5 mm indicates an ACL rupture (9, 371, 372). Although, others have defined a graft failure as a side-to-side difference of > 3mm and not 5 mm (372). Anterior translation was measured with application of 20 pounds in millimeters of excursion. Care was taken to ensure reliable and accurate measurements with consistent arthrometer placement and the patient always in the supine position. Both legs were placed on a thigh support with a strap to keep them in a neutral position. The knees were in 30° of flexion and the patient was asked to relax. The measured difference between the surgical and contralateral leg, in millimeters of displacement, were used in the analysis. Measurements were excluded from analysis if the contralateral leg possessed a greater ligament laxity than their reconstructed limb. One male participant was excluded from the statistical analysis for that reason.

Functional measurements

Functional deficits were based on the measurements of hop distance (single leg or cross-over hop) on the surgical limb compared to the contralateral noninjured limb. A limb symmetry index (LSI) was calculated by dividing the value for the involved/uninvolved limb (*100). The clinical requirement for normal function is considered 85% - that is, the involved limb should be functioning 85% as well as the uninvolved limb (41, 59). Hop testing has shown to be a reliable and valid performance based measurement following ACL reconstruction and has been validated for facilitation in research and clinical practice (182, 373).

Before attempting the functional measurements each subject was allowed a five-minute warm-up on a treadmill. A verbal description and a physical demonstration were given prior to each functional test. Vocal encouragement was provided during and between trials as a means to motivate subjects to give their best effort.

Single Leg Hop

The subject was asked to execute a single leg hop for distance by starting on one foot, with their toes up to the taped line. From that starting position they were asked to hop as far forward as possible. Subjects were not discouraged from using their arms since they were asked to perform at maximal efforts. The distance was measured from the taped line to the back of the heel as is commonly done in track and field and controls for the variation of individual foot size. Subjects were allowed three trials with the greatest distance measured in centimeters used in the statistical analysis.

Single Leg Crossover Triple Hop

The single leg crossover triple hop was conducted in a similar manner as the single leg hop. The subject was asked to hop as far as possible on one leg while completing 3 consecutive hops; the second and third hops required crossing over and back over a taped line (9.8 cm). The subject was given personal preference as to which side to hop to first. Participants were encouraged to stay close to the taped line when crossing over to prevent wasting valuable distance in the horizontal direction.

Retro Step (Figure 5-1)

The retro step test (62) is commonly used to diagnose patello femoral pain (PFP) (63, 64) but has not been traditionally applied to ACL patients. The retro step requires the high demand of balance and stability as well as the motor ability to step backward at increasing heights. Given the similar neuromechanics between PFP and ACL reconstruction, along with our clinical experience showing this test is sensitive for assessing functional limitations in patients with PFP, we included the retro step test in this study.

The retro step test was conducted using an aerobic step platform starting at 4 inches high. The participant was instructed to stand facing away from the step and place one foot on the step with the other foot on the floor. They were instructed to slowly push off and extend their knee without using the foot on the floor until the leg on the step was straight. After achieving that position the subject slowly lowered their free leg to the floor while maintaining a level pelvis with hands on their hips. Additional 2 inch blocks were added for height until failure or until stop criteria occurred. Stop criteria included loss of balance, prolonged weight bearing by foot on floor, using grounded foot to push off, and hiking of either hip. Scores were recorded in inches with the highest step height completed used in the analysis.

Figure 5-1. Retro Step test

Questionnaires

The IKDC (International Knee Documentation Committee) and KOOS (Knee and Osteoarthritis Outcome Score) questionnaires were administered. These subjective questionnaires are commonly used in clinical practice and have been validated against numerous populations with variable diseases and length of time and at differing ages and activity levels as well as populations having treatment procedures as a result of knee complaints (374-377).

The IKDC asseses the level of function and level of pain, stiffness, swelling, knee lock, and the knee giving related to function for activities of daily living and sports in patients with a knee injury. A mark of 100 is understood to denote no limitation with activities (sports activities and daily living) and a complete lack of symptoms related to knee injury. KOOS measures the subject's attitude about their knee as well as related problems such as hearing grinding in the knee, ability to straighten and bend the knee, amount of pain when going up stairs, difficulty going shopping, ability to run and amount of confidence in the knee. A mark of 100 is understood to denote a complete lack of symptoms and a score of zero is suggestive of severe symptoms (375, 376). KOOS scores were reported by subscale (Pain, Symptoms, Function in Daily Living, Function in Sport and Recreation, Knee Related Quality of Life).

5.3 Data Analysis

All data were first cleaned and checked for outliers and missing values. The LSI ([(surgical/non-surgical)*100] was calculated for the three functional measurements to express relative function of the surgical limb relative to the healthy limb. Mean and standard deviations were calculated for all outcome variables overall and by gender.

5.4 Results

Data were collected on a total of 25 men and 38 women who ranged in age from 19 to 63 years of age. Descriptive characteristics for all participants are presented in Table 5-1. The participants ranged in height between 156 to 191 cm and a weight range of 52 to 165 kg. Out of the 63 participants 43 had a bone-patella-bone graft (BPTB autograft), 9 had a hamstring tendon autograft, and 11 had a donated patellar tendon from a cadaver (bone-patella-bone allograft) to replace the torn ACL. Time elapsed between injury and surgical reconstruction ranged from 2 weeks to 3.5 years and an average of 4.5 years post surgery.

Table 5-1. Descriptive characteristics for male and female patients with a history of ACL reconstruction. Values are Mean (SD).

	Overall	**Male**	**Female**
N	63	25	38
Age	28.5 (10.6)	32.7 (9.7)	25.9 (10.3)
Weight (kg)	76.3 (16.8)	82.5 (9.6)	72.3 (19.3)
Height (cm)	170.2 (16.4)	179.7 (6.3)	164.0 (17.9)
Time since surgery (yr)	4.5 (3.3)	4.3 (3.0)	4.6 (3.5)
Type of surgery (% patella)	68.3%	24.0%	13.2%
Type of surgery (% hamstring)	14.3%	56.0%	76.3%
Type of surgery (% allograft)	17.5%	20.0%	10.5%
IKDC	87.3 (9.7)	85.0 (9.2)	88.7 (9.8)
Symptoms subscale	62.4 (8.7)	58.2 (9.4)	65.2 (7.2)
Pain subscale	92.6 (6.8)	91.0 (6.4)	93.8 (6.9)
Function of Daily Living subscale	97.7 (3.5)	97.4 (3.0)	97.8 (3.9)
Function of Sports & Recreation subscale	83.0 (13.9)	80.6 (12.8)	84.5 (14.5)
Quality of Life subscale	76.2 (16.3)	70.6 (14.1)	79.7 (16.8)

Ligament laxity and subjective outcomes

Twenty (32.3%) of the subjects in this study had > 3 mm of excursion, while 34 of our 63 participants had < 3 mm of excursion. Of those with ≤ 3 mm excursion, 14.3% had <1mm, with the majority (64.3%) scoring between 1-2 mm.

Subjective scales (Table 5-1)

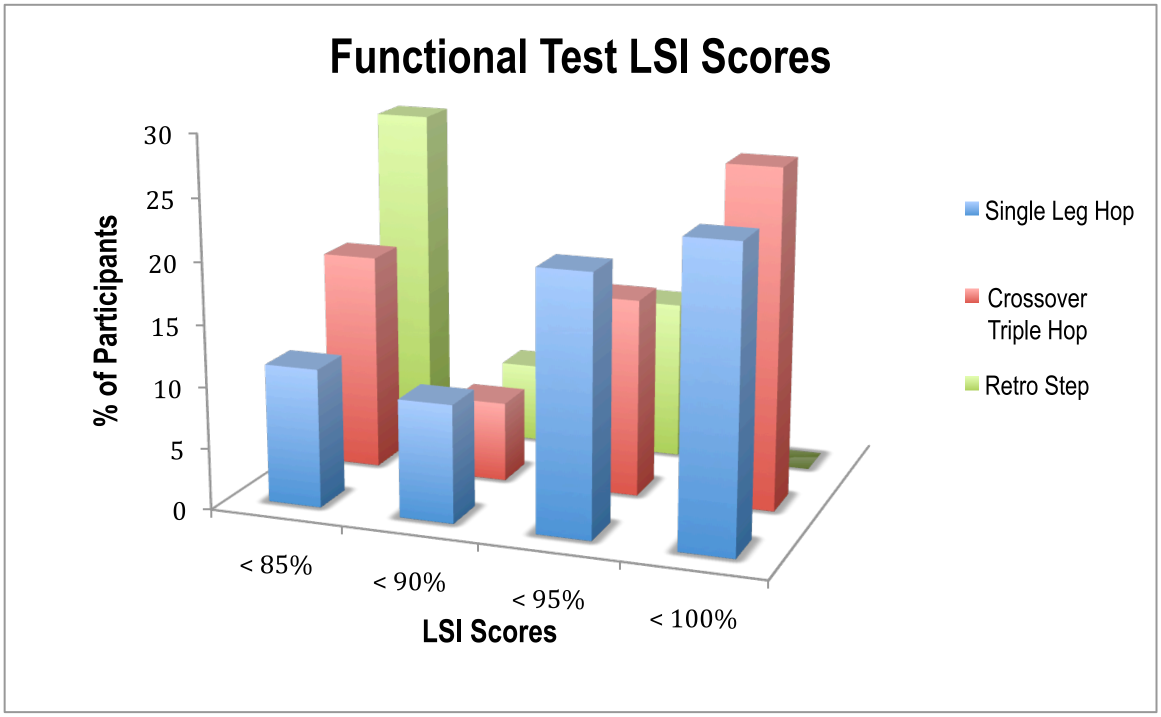
The IKDC subjective questionnaire was used to evaluate level of function and level of symptoms. The IKDC scores ranged between 55.0 – 100. The KOOS questionnaire demonstrated lower scores for the symptoms subscale ranging from 39.0 – 79.0, knee related quality of life subscale between 31.0 – 100, and function in sport and recreation subscale ranged from 45 – 100. In contrast, the function in daily living subscale ranged from 84 – 100 and pain subscale between 72 – 100, were rated nearly perfect. Although the correlations were not strong, the IKDC ($r = 0.26$, $p = 0.04$) function in sport and recreation subscale ($r = 0.29$, $p = 0.02$) and quality of life subscale ($r = 0.25$, $p = 0.04$) were significantly associated with the single leg hop. The crossover triple hop test had a significant relationship with the IKDC ($r = 0.29$, $p = 0.02$), symptoms subscale ($r = 0.29$, $p = 0.02$) and the function of daily living subscale ($r = 0.32$, $p = 0.01$) (Figure 5-4).

Functional measurements (Figure 5-2)

The mean functional scores for the groups showed normal LSI scores. However, there were still a number of patients that performed below normal values, which implies that the surgical knee for those individuals is not functioning at a level to return to play.

A single leg hop was executed in order to examine lower extremity function. Out of the 63 participants, only 7 were less than 85%. In addition to the single leg hop, the triple hop was used as a more demanding measurement to examine lower extremity function. In this group of participants almost 18% performed below 85%. The retro step test was found to be the most difficult functional measurement. Almost 30% of the participants in this study were unable to perform greater than 85%.

Figure 5-2. Percentage of participants with limb symmetry index scores below 85%, 90%, 95% or 100% for the single leg hop, crossover triple hop and retro step test



5.5 Discussion

The present study aimed to observe differences in leg side-to-side functional ability of ACL patients 1- 18 years post ACL reconstruction. Depending on the test used, 11 - 30% of our participants performed below normal values and 20 of our 63 participants had > 3 mm of excursion on ligament laxity. The subjective measurements demonstrated the poorest scores for the symptoms subscale, knee related quality of life subscale, and function in sport and recreation subscale. In contrast, the function in daily living subscale and pain subscale scores were quite high. Thus, ACL patients in the long term may have implications for return to play and quality of life.

KT-1000 Ligament Laxity

Twenty (32.3%) of the subjects in this study had > 3 mm of excursion at an average of 4.5 years post-surgery. In contrast, Keays et. al. (9) found that pre-injury stability restored for the majority of their patients (~80% $\leq$ 3 mm) 6 years post surgery. In a separate study, Yamaguchi et al. (40) showed an average laxity score of 4 mm 13 years post-surgery with results more consistent with our study. These studiess suggest that laxity scores may actually increase with greater time since surgery, but then remain steady in the long-term (9, 40). In our study, we found no association between time since surgery and laxity score (r = -0.09, p = 0.52), however, this should be explored in long-term prospective studies. Despite the importance of proper stability and range of motion of the knee joint, our results also demonstrated no associations between the functional tests and knee laxity as well as the subjective questionnaires. Prior studies have reported both significant (335) and nonsignificant (136-138) correlations between the single leg hop and laxity. Additionally, it has been demonstrated that subjective function is connected to ligament laxity (378).

Single Leg Hop

We used a number of tests to assess functional ability in patients with ACL reconstruction. Of those, the single leg hop test is the most commonly reported assessment of lower extremity function in this population. Typically, scores from the injured leg are compared to the non-injured leg and a score of 85% on the injured leg is generally accepted as 'normal'. Data collected on the normal population demonstrated that limb symmetry of equal to or greater than 90% was normal for males and equal to or greater than 80% was normal for females (170). For the single-leg hop test, it has been reported that the ability to hop 80 – 90% of one's height is considered normal for males, whereas the capacity to hop 70 – 80% of one's height is deemed normal for females (171). Or the ACL patient should have the capacity to perform within 10% of their non-surgical limb (171).

Consistent with previous studies (9, 379), a majority (89%) of participants in our study had an LSI above 85% for the single leg hop test. Some authors have proposed that the single leg hop test is not a sensitive enough measure of function in this population (41-44). However, it is advised that more complicated tests might cause re-injury (42); hence, there must be a balance between safety and test effectiveness. In contrast, other authors have reported as much as 43% - 47% of patients with LSI below 85% on the single leg hop test (47, 61). Well Pinczewski et. al. showed at 10 years post surgery, 13 - 20% of the participants were unable to perform a single leg hop at > 90% of their healthy limb (38).

Single Leg Crossover Triple Hop

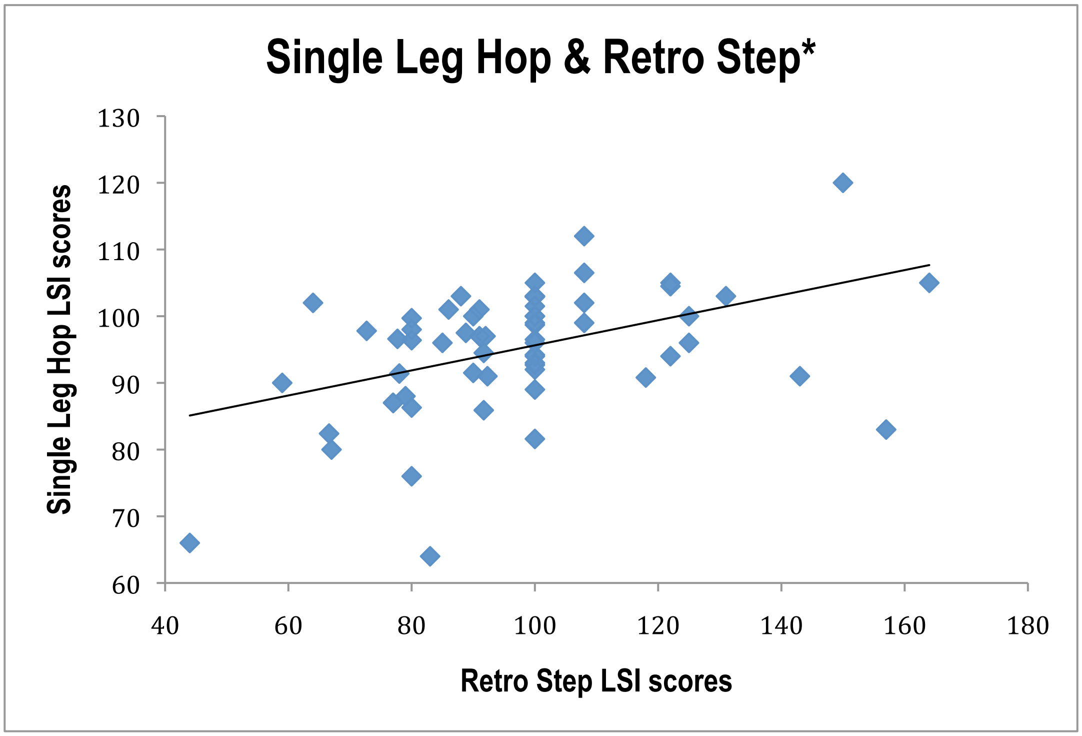
The single leg cross over triple hop test was used as a more demanding assessment of lower extremity function and qualitative strength recovery. In our population, the triple hop test identified more (18%) patients with low LSI's than the single leg hop test. Optimal function following ACL reconstruction is dependent on many factors, of which muscle strength is one of the most important (175). Thus, a possible explanation for asymmetric function may simply be due to the decrease in quadriceps strength rather than implying functional deficits (167, 172, 175). In contrast, others (138, 378) have reported low correlations between the single leg hop, not the crossover triple hop, and muscular strength. Possibly, the single leg hop test may only produce qualitative evidence of muscular strength recovery compared to isokinetic dynamometer testing equipment (138).

Another factor that may influence functional outcome is the graft type. Keays et. al. (9) demonstrated lower quadriceps strength on the injured leg compared to the non-injured leg for the BPTB group at 6-years post-surgery. The majority of our participants (68%) were also repaired by the BPTB graft. Additionally, it has been reported that BPTB grafts affect the degeneration process of the muscles to a greater extent than hamstring grafts (343). Similarly, it was shown that the hamstring donor site group out performed the patellar tendon donor site group on the crossover triple hop (9). Our study showed no evidence of a difference in functional outcomes between graft types, however, our study was not powered to detect differences among graft types.

Retro Step

The retro step has rarely been used with ACL patients, instead it has been commonly used with patello femoral patients (PFP) (62-64). In our study, the retro step test showed deficits in a greater portion of the population than standard hop tests suggesting it is more sensitive than the single leg hop and crossover triple hop tests in detecting functional deficits in patients with ACL reconstruction. Almost 30% of the subjects in this study were unable to perform greater than 85%. Additionally, the retro step LSI scores were found to significantly correlate with the LSI scores of both the single leg hop ($r = 0.44$; $p < 0.001$) (Figure 5-3) and crossover triple hop ($r = 0.39$; $p < 0.001$). This test requires high demands of balance and stability as well as the motor ability to step backward at increasing heights and thus, may be a useful test to include in clinical settings.

Figure 5-3. Illustration of the correlation between the retro step test and the single leg hop



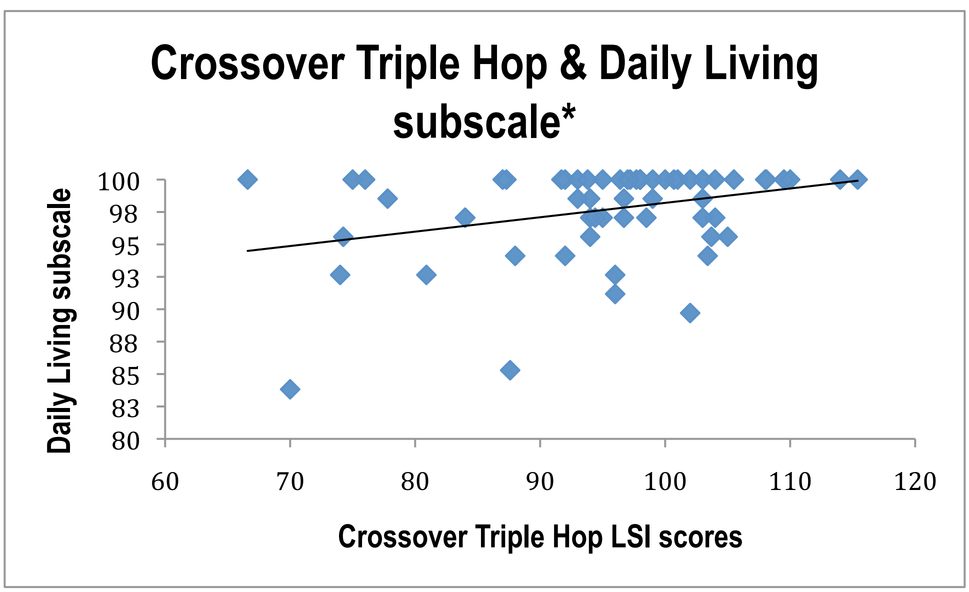
*$r = 0.44$; $p < 0.001$

Questionnaires

Overall the mean IKDC subjective score was 87.3 (range, 55 – 100) in our sample. Compared to normative data (380), our participants scores were lower than individuals with no knee problems, treatments or surgeries of the same gender and age group (male range between 93.1 – 95.5; female range 90.7 – 93.4). The KOOS questionnaire demonstrated low scores for the symptoms subscale, knee related quality of life subscale, and function in sport and recreation subscale. Kvist et. al. (4) studied the fear of re-injury as an obstacle for coming back to athletics after ACL reconstruction and reported a high percentage of participants with a strong fear of re-injury. In that study, poor knee related quality of life was strongly correlated with a fear of re-injury (4). Many of our participants still had not fully recovered their subjective satisfaction 1 to 18 years after surgery, which could be associated with a fear of re-injury. However, we did not explore that association in this study.

Interestingly, we demonstrated significant associations between the functional tests and subjective questionnaires. Subjective scores have been shown not to correlate to quantified function and strength scores in athletes with ACL injuries and reconstructions (187-189). Barber et. al. (41) reported that despite normal range on the one-legged hop tests, subjective questionnaire results reported that these patients had experienced giving-way episodes with sports activities. A possible explanation suggested for the lack of associations were that functional tests studied are performed under strictly controlled clinical conditions. Additionally, due to the number of different subjective questionnaires makes it difficult to compare studies. Determining a consensus of the relationship between functional and subjective scores, why those results occur and what are the implications of the determined relationship requires further exploration.

Figure 5-4. The functional tests significantly correlated with the subjective questionnaires. Below the crossover triple hop and the function of daily living subscale are shown.



*$r = 0.32$; p 0.01

5.6 Conclusion

In conclusion, this study showed that differences in leg side-to-side functional ability and poor subjective scores do occur up to 18 years after ACL reconstruction. Future long term prospective studies will increase our current understanding of long term recovery and may change and improve the patients' and sports medicine professionals' choice of management; foundation for design and implementation of effective rehab programs as well as exercise prescription for the ACL patient. Additionally, we introduced the retro step test, which resulted in the greatest proportion of our participants scoring below 85% compared to the other 2 functional tests. Future studies should test the specificity and sensitivity of this test to determine its validity as a useful ACL functional test.

6

SUMMARY

In conclusion, the objective of this dissertation was to explore the bone geometric adaptations and functional outcomes after ACL reconstruction both cross-sectionally and prospectively. The findings described in Chapters 3, 4, 5 begin to elucidate the consequences of ACL reconstruction on bone strength and geometry and functional outcomes. This dissertation adds a novel addition to the literature in 3 distinctive aspects. The primary feature was the exploration of muscle and bone adaptations as a result of the change in mechanical loading via measurements of bone volumetric density, geometry and estimates of strength. Subsequently, exploring bone volumetric density, geometry and estimates of bone strength in ACL reconstructed patients prospectively is new to the ACL literature as well as it begins the support of evidence of a reliable following of the development of recovery, or time line of muscle comparative to bone. Lastly, we reported long-term data of direct assessments of functional outcomes in patients with a history of ACL reconstruction. Below I review the results of each manuscript relative to the initial aims and hypotheses.

Specific Aim 1 was to explore the effect of ACL reconstruction on bone strength and muscle size of the surgical compared to non-surgical legs. I *hypothesized* that bone strength would be significantly lower in the surgical compared to non-surgical legs 1-5 years post surgery at sites nearest the injury (proximal tibia, patella and distal femur), whereas sites further from the injury would have no differences between the surgical and non-surgical legs. I also *hypothesized* that there would be no differences in muscle size between the surgical and nonsurgical legs.

As demonstrated in Chapter 3 our findings are with our hypothesis. The mean %difference analysis showed that overall all bone outcomes were lower in the surgical leg particularly at sites closest to the injury. Muscle CSA was similar between sides at both the tibia and femur. At the patella, BSI, cortical area, section modulus and cortical density were all significantly lower. These findings feature the support of previous DXA studies reporting bone loss after ACL surgery and theorizes that geometric adaptations may be an important component to an ACL patient's musculoskeletal health.

Specific Aim 2 was to explore *changes* in muscle size and bone strength for 9-months following ACL reconstruction. I hypothesized that bone strength will continue to decrease at sites nearest the injury (proximal tibia, patella and distal femur) through 4-months. I also hypothesized that muscle cross-sectional area will also decrease over 4-months post surgery.

As demonstrated in Chapter 4 our findings are with our hypothesis. The bone strength continued to decrease at sites nearest the injury (proximal tibia, patella and distal femur) through 4-months. Muscle cross-sectional area did decrease over 4-months post surgery. Compressive strength (BSI) deficits were evident at tibia 86%, patella and femur 4% as well as trabecular density at tibia 86%, patella and femur 4%. These findings highlight the need for prospective longitudinal studies to explore if ACL injury and reconstruction have significant implications for optimal musculoskeletal health.

Specific Aim 3 to describe both subjective and clinical functional outcomes in patients with a history of ACL reconstruction as well as explore clinically useful tests of function in this population. I *hypothesized* that there would be approximately 30% of our participants who score below normal on functional tests and subjective questionnaires. I also *hypothesized* that that the retro step test would be more difficult for a greater number of participants than the standard functional tests.

As demonstrated in Chapter 5 our findings are with our hypothesis. On the single leg hop, the single leg crossover hop, and the retro step, 11%, 18%, and 30% of the participants, respectively had LSI's below 85% for each test. Twenty of the subjects had > 3 mm of excursion on the KT-1000 ligament laxity assessment. Compared to subjective normative data, our participants scores were lower than individuals with no knee problems, treatments or surgeries of the same gender and age group. These findings highlight that differences in leg side-to-side functional ability and poor subjective scores do occur 1 - 18 years after ACL reconstruction as well as the retro step test was more difficult for a greater proportion of the participants than the standard functional tests. Future studies should test the specificity and sensitivity of this test to determine its validity as a useful ACL functional test.

7

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