DESIGN AND EVALUATION OF A PROSTHETIC ANTERIOR CRUCIATE LIGAMENT REPLACEMENT MEDICAL DEVICE

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DESIGN AND EVALUATION OF A PROSTHETIC ANTERIOR CRUCIATE LIGAMENT REPLACEMENT MEDICAL DEVICE

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SUMMARY

Rupture of the anterior cruciate ligament (ACL) is a relatively common sports-related injury for which the current treatment is reconstruction with an autograft or allograft. Drawbacks associated with each of the current options would make a prosthetic alternative advantageous, however, artificial ligaments are not widely used, having failed due to lack of biocompatibility and mechanical insufficiencies. To develop the next-generation prosthetic ACL, design control principles were applied including specification of comprehensive design inputs, risk analysis, and verification testing. A design was proposed utilizing polyvinyl alcohol and ultrahigh molecular weight polyethylene, selected for good biocompatibility and mechanical strength and stiffness suitable for ACL replacement. A biomimetic fibrous rope pattern was designed for the intra-articular ligament section of the prosthetic that produced a close match the static tensile behavior of the native ACL and which also demonstrated good resistance to fatigue and creep. A calcium phosphate coating was recommended for the sections of the device lying within the bone tunnel to increase the rate of osseointegration. The proposed design was then evaluated in a computational simulation to assess functional restoration and the effects of installation parameters such as tension and tunnel orientation on knee kinematics. The encouraging results of preclinical verification testing support further *in vivo* evaluation of the proposed design.

CHAPTER 1 Introduction

1.1 Anterior cruciate ligament – anatomy and function

Ligaments are soft-tissue structures that connect bones to other bones forming a joint. The anterior cruciate ligament (ACL) resides within the knee and extends from a posterior position on the medial wall of the lateral femoral condyle to an insertion at the anterior part of the central tibial plateau. As a tensile load bearing structure, the ACL functions as the primary restraint to anterior translation of the tibia relative to the femur and also has a secondary role in limiting internal tibial rotation. It is a critical component for the stabilization of the knee joint throughout its range of motion.[1-2]

The ACL is a band-like structure of dense connective tissues, irregular in shape with a length ranging from 22 to 41 mm and a width from 7 to 12 mm.[1] Native ACL is comprised of crosslinked, parallel collagen bundles (types I, III, and V), water, elastin, proteoglycans, and cells.[2] The collagen fibers provide high tensile strength, withstanding cyclic loads between 0 and 450N on the order of one million cycles per year.[3-5] The maximum load and linear stiffness of the native ACL has been reported to be from 1725 to 2160 N and from 182 to 292 N/mm, respectively.[6-8] The Young's modulus of human ACL is 111 MPa and the ultimate tensile strength is at least 38 MPa.[9-10] A periodic crimped pattern along the length of the collagen fibers results in a low stiffness toe region at low levels of strain.[5]

1.2 ACL rupture and current reconstruction options

ACL rupture is the most common knee ligament injury and is most often caused by the sudden twisting of the knee in a weight bearing position.[11] Annually, approximately 1 in 3000 Americans experience anterior cruciate ligament injury.[12-13] Approximately 50,000 ACL reconstructions are performed each year in the United States

at an average cost of $17,000 per procedure corresponding to a total financial impact of nearly 1 billion dollars.[14] The untreated ruptured ACL can result in knee pain, loss of stability, increase risk of meniscal injury, and an accelerated onset of osteoarthrosis.[11-12]

Unlike collateral knee ligaments which heal after injury and generally respond well to conservative treatment, the ACL does not heal when torn, because it lacks significant vascularization and has a limited blood supply. Damage to its surrounding synovial lining leads to blood dissipation within the joint preventing formation of a local hematoma.[12] Therefore, surgical reconstruction is the standard treatment for ACL rupture, in which a ligament replacement is secured between tunnels drilled into the femur and tibia.[15] Fixators, such as screws, buttons, or crosspins, are used to attach the ends of the ligament replacement within the bone tunnels at the time of surgery and over time these tunnel sections of the replacement integrate with the surrounding bone.[16] The aims of reconstruction are to restore the kinematics and stability of the injured knee and also to prevent future degenerative changes.[15] Patients with ACL injuries tend to be younger and more active than other orthopedic patients, and therefore, reconstructions should exhibit good longevity, withstanding high stresses over millions of cycles.[17]

Autologous graft substitutes, or autografts, come from the patient's own body and provide advantages such as the presence of stretch receptors, vascularity, and the absence of graft rejection issues. The bone-patellar tendon-bone (BPTB) and the double-looped semitendinosus/gracilis tendon (DLSGT) hamstring autografts (also called quadrupled hamstring grafts) are the most popular types of autografts, used in over 90% of ACL reconstructions. The quadriceps tendon and iliotibial band have also been used as graft sources though are not as common.[1, 17] Problems with these

grafts include post surgical knee pain, flexion contracture, and crepitation. Issues relating to donor site morbidity, specifically arthrofibrosis, patello-femoral pain when kneeling, quadriceps weakness, and loss of sensitivity associated with BPTB grafts have caused a gradual shift away from their use to the DLSGT grafts in recent years.[1] Overall donor site morbidity with hamstring grafts is generally less than with the patellar tendon grafts, however saphenous nerve damage and hamstring weakness have been reported.[18] Other disadvantages of autograft reconstructions include longer operation and recovery times due to the necessity of the additional harvesting procedure.

The use of allografts, made from the tissue of a cadaver, circumvents the problem of donor site morbidity; however, is associated with other drawbacks including risk of immunological rejection and disease transmission, delayed biological incorporation, and a limited supply of donor tissue.[17] Allografts cannot be sterilized completely without compromising their mechanical properties, and are, therefore, either more susceptible to failure or associated some risk of disease transmission.[17, 19] Increasing demand and a low supply of young healthy cadaver donors with low risk lifestyles have resulted in a shortage of allograft tissues, making allografts very expensive, costing from $2000 to $10,000 each in addition to the cost of the procedure. Surgeons have also been forced to use alternative cadaveric tissues such as the Achilles tendon, and the anterior tibialis and posterior tibialis tendons due to this lack of availability. Additionally, many surgeons do not have ready access to allograft procurement and processing facilities. Allografts are more often used in repeat reconstructions when autografts are no longer available for harvest.[17]

Artificial ligaments have been proposed as an alternative to overcome the shortcomings of biological grafts. Past devices have been made from a wide range of materials including carbon fibers, polytetrafluoroethylene, polyethylene terephthalate,

polyester, polyurethane urea, and polypropylene, none of which have been able to provide satisfactory long term results due to mechanical and biocompatibility insufficiencies.[11] The use of carbon fiber, Dacron, or polypropylene fiber yarn prostheses is associated with chronic inflammation and the generation and migration of wear particles in the joint space and lymph nodes. Excessive creep, wear damage, fatigue, and high rates of rupture leading to persistent joint laxity have also been reported several years after implantation with carbon fiber, polytetrafluoroethylene, polyethylene terephthalate, and polyurethane urea prosthetics. Autografts and allografts have consistently been more durable and resistant to mechanical failure than the many biomaterials used to make prosthetics.[17]

Tissue engineering an ACL by culturing progenitor ligament cells on a matrix scaffold is currently in the research phase. This approach would involve seeding the scaffold with ACL fibroblast progenitor cells and applying mechanical loading and chemical cues to stimulate the cells and tissue to mature in the correct orientation, replicating a normal ACL's structure and geometry. Current results of histological studies on tissue engineered ligaments indicate that neoligamentous ingrowth occurs, however mechanical testing of the new tissue reveals insufficient strength and stiffness, often by one or more orders of magnitude. Challenges associated with regenerating ligaments with the collagen organized in the appropriate orientation to provide the specific mechanical response requirements will prevent such treatment options from reaching clinical implementation in the near future.

1.3 Developing a prosthetic alternative

The focus of this thesis is the development of a next generation ACL replacement, free from the problems associated with currently used treatment options, made possible with recent advances in biomaterials and understanding of knee and

ligament biomechanics. The ACL replacement will need to sufficiently match the mechanical properties of the native ACL in terms of strength, elasticity, and durability without excessive creep and fatigue or side effects such as immunogenic particulation. Furthermore, the device should preserve the kinematics of the native ACL, provide the needed knee stability, and limit wear in the joint to reduce the progression of osteoarthritis.

Each of the following chapters addresses a different aspect of the development of the device. Chapter 2 describes the design considerations as a whole within the context of a structured, medical device-focused design control process. Comprehensive design inputs for the device are specified together with appropriate verification tests. A risk analysis and design recommendations are also presented. Chapter 3 focuses on the intra-articular section of the prosthetic and how to reproduce the unique mechanical behavior of the ligament. Fibrous materials and rope structures are first tested in tension to converge upon a design that produces the correct static response. Then, the design is subjected to cyclic loading to test long-term behavior, specifically the resistance to fatigue and permanent elongation. Chapter 4 focuses on the bone tunnel sections of the device and reviews some potential strategies and substances used to improve healing and osseointegration such the calcium phosphates, various growth factors, cells, and periosteum. Previous studies on the effectiveness of these bioactive materials were compared to determine which, if any, would be advantageous to incorporate into the design of the prosthetic. Chapter 5 moves beyond the device design phase to a functional evaluation of the device in a knee model. Simulated kinematic tests were executed to measure functional restoration provided by the device and predict *in vivo* stress concentrations. The effects of tunnel orientation and device tension were also assessed so that recommendations could be offered

regarding how the device should be installed. Together, these chapters aim to provide adequate preclinical evidence for feasibility and design verification to proceed with clinical evaluation. Chapter 6 concludes the thesis by highlighting the significance and potential impact of this research and outlining the next stages of product development and the requirements for market entry.

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CHAPTER 2 Design Considerations for a Prosthetic Anterior Cruciate Ligament

2.1 Introduction

The anterior cruciate ligament (ACL), one of the four major ligaments in the knee, is a critical component for the maintenance of proper tibiofemoral orientation, knee motion, and knee stability.[1-2]. The ACL extends from a posterior position on the medial surface of the lateral femoral condyle to a more medial and anterior position on the tibial plateau. In this orientation, the ligament acts as a tensile load bearing structure, resisting excessive anterior translation of the tibia relative to the femur.

The mechanical behavior of the native ACL, the determining factor influencing its function within the knee, is derived from the material composition and structural organization of the tissue. Extracellular matrix (ECM) comprises approximately 80% of the ligament by volume.[3] The ligament ECM can be modeled as a fiber-reinforced composite structure, in which multiple, densely packed, bands of collagen fibers are aligned axially in parallel, embedded within a hydrophilic ground substance.[2, 4-8] The collagen fibrils, which constitute approximately 75% of the dry weight of the ligament, provide high ultimate strength and exhibit a periodic, crimped pattern resulting in nonlinear, strain-hardening behavior: the ligament deforms easily at low strain in the so-called “toe” region which is followed by greater stiffness at higher strain. [1-2, 4]

ACL rupture is a relatively common sports injury, which can occur when the knee is subjected to combined twisting and compressive forces, when the knee is hyperextended, or when an external force is applied in the anterior direction on the tibia. [9-10] ACL injuries have been observed across the mid-substance of the ligament, at the interface between the ligament and bone, or in the bone close to the ligament

attachment site.[10] Ligament damage often results in excessive anteroposterior laxity and knee instability.[11-12]

2.2 ACL reconstruction

Due to sparse vascularization and low blood supply, the torn adult ACL has not been observed to heal without treatment or with primary repair.[4, 13] Consequently, the current treatment options are limited to reconstructions, where a ligament-replacing autograft or allograft is installed between the femur and tibia, fixated within bone tunnels, with the primary goal of providing stability and restoring function to the knee.[14] Approximately 175,000 ACL reconstructions performed each year in the United States at a cost exceeding $2 billion.[15-17] A meta-analysis of the clinical results of ACL reconstruction reveals that 64% to 75% of patients return to pre-injury levels of activity 2-years post-operation.[18] The prevalence of re-rupture failure is reported to be 3-4% with an additional non-rupture complication rate of 12%.[18]

The femoral tunnel can be drilled transtibially or through an auxiliary anteromedial portal.[19] Placement of the transtibially drilled femoral tunnel is constrained by the fact that it must be collinear with the tibial tunnel with the knee at the position at which it is drilled, commonly at 90° of knee flexion.[20] If the femoral tunnel is drilled transtibially, the resulting position of the graft is more vertical, and the femoral tunnel entrance tends to lie towards the roof of the notch, anterior to the footprint of the native ACL.[20] Grafts suspended from transtibially drilled tunnels may be effective at resisting excessive anterior tibial translation, however, are more likely to result in positive pivot shift and greater rotational laxity.[21-23] An alternative is the anteromedial portal technique where the tibial and femoral tunnels are drilled independently, the latter from an auxiliary anteromedial portal at the medial side of the patella with the knee at 110° to 130° flexion.[24] This anteromedial technique results in a more lateral position for the

femoral tunnel entrance closer to the center of the native footprint improving rotational stability.[21-22, 25]

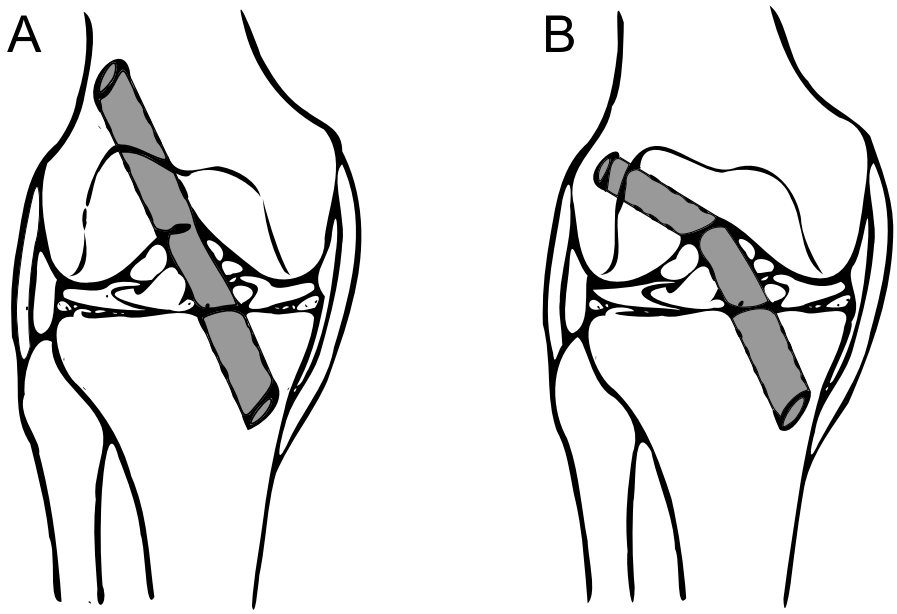

Figure 2.1 Transtibial (A) and Anteromedial portal (B) drilled femoral tunnel orientations

An autograft or allograft is attached to the bone tunnels at the time of installation with some type of fixation device, which may vary with the graft type, tunnel placement, patient-specific knee characteristics, and surgeon preference.[26-28] Cross-pins and buttons are examples of suspensory types of fixations, where the graft is secured closer to the extra-articular end of the tunnel away from the joint.[29] Alternatively, interference screws may be used to fix the graft at the aperture near the intra-articular space.[28] The initial fixator must provide sufficient strength to support the graft from the time of installation until the completion of osseointegration.[30] The rehabilitation protocol is designed to protect the joint early on by limiting knee activity to operations producing loads not exceeding the graft fixation strength until stronger integration with the bone forms over time.[30]

2.3 Biological grafts

Autograft reconstruction is a popular option in which a section of the patient's own tissue is harvested and utilized as a ligament replacement, most commonly from the patellar tendon or hamstrings. Autografts have several drawbacks. Donor site morbidity such patellar fracture, nerve damage, infection, and soreness are reported by 40% to 60% of patients in the years following autograft reconstruction.[31] Additionally, the requirement of the harvest procedure in addition to the installation procedure increases the total operation time and cost.[32]

Allografts, harvested tissue from a cadaver, are also used for ACL reconstructions as an alternative to autografts. Allograft usage precludes donor site morbidity and the necessity of the harvest operation, however is associated with other drawbacks. The use of allografts results in abnormal knee stability in approximately 14% of cases versus only 5.3% with autografts, as defined by the International Knee Documentation Committee (IKDC).[33] Allografts are also slower to incorporate within the bone tunnels.[33-35] Furthermore, allografts are associated with a disease transmission rate as high as 4%.[36] A 2002 publication from United States Centers for Disease Control and Prevention (CDC) reports 26 cases of infection from allografts and one fatality from *Clostridium sordellii* contamination.[37] Seventy cases of infection were further reported in a 2004 CDC report.[38]

2.4 Prosthetics as an alternative

A synthetic prosthetic device to replace the ACL would be advantageous as it would preclude the donor site and infectious problems associated with the biological grafts. Operation times would be reduced and the operation made less invasive relative to autograft reconstructions, since the harvest procedure would not be required. By eliminating the need for additional operating room time, anesthesia, and an overnight

stay in the hospital, the cost of the procedure could be reduced by more than $1,000.[32] Additional costs associated with the use of allografts include more expensive fixation and the price of the graft itself, which together can exceed $750.[32] After the operation, biological grafts undergo collagen remodeling, during which the mechanical properties of the graft change extensively, with strength and stiffness reducing by 50 to 80 percent after six weeks before slowly increasing to restore functional laxity over the next 24 to 52 weeks.[39-40] A prosthetic device can be designed to retain its strength and stiffness in the early weeks and therefore may not require as long a time for recovery.[40] There have been three general approaches to reconstruction of the ACL using polymeric materials.[41] Frank replacement type prostheses are designed to permanently replace the ACL. Stents, also called ligament augmentation devices (LADs), are designed to protect autografts during the earlier stages of revascularization and maturation. Finally, scaffold type devices aim to provide support for new, regenerated or engineered tissue.

The earliest record of reconstruction of the ACL with a non-biological graft was F. Lange's attempt with silk braids in 1903 which failed quickly.[42] In subsequent years, metal wires, nylon, silk, and other materials were suspended in place of the ligament, but recurring mechanical failures and lack of biocompatibility limited such development to the animal testing stage.[43] A newer generation of prosthetics were developed from the 1970s through the 1990s, made from a wide range of materials including carbon fiber, polytetrafluoroethylene, polyethylene terephthalate, and polypropylene.[44] In the late 1980's the United States Food and Drug Administration (FDA) approved the Gore-Tex (W.L. Gore, Flagstaff, Arizona) and Stryker-Meadox Dacron (Meadox Medical, Oakland, New Jersey) frank replacement devices, as well as the Kennedy LAD (3M, St. Paul, Minnesota); however, none of these are currently used.[45]

Carbon fiber was explored as a possible material for ACL replacement, but was observed to fragment and appear in the regional lymph nodes.[46] The ABC prosthetic ligament (Surgicraft Ltd., Redditch, UK), consisting of carbon fiber and polyester, had unacceptably high rates of creep and complete rupture leading to poor results.[47] Good Lysholm scores, defined as greater than 76 out of 100, were achieved in only 41% of patients after 1 to 3 years.[47] The Stryker-Meadox Dacron graft, made of polyester with a velour coating, failed to maintain knee stability in 40% to 60% of patients after 4 years as assessed by pivot shift, side-to-side laxity, anterior drawer, and Lachman test.[48-49] Failures were attributed to elongation due to creep and ruptures occurring at the femoral insertion, tibial insertion, and the central body of the graft.[50] The Gore-Tex graft, made of expanded polytetrafluoroethylene, had good initial results, but were later observed to cause four types of failures: (1) effusions and chronic synovitis from particulate debris or disrupted exposed fibers, (2) graft rupture after cyclic loading, most commonly on the femoral side, (3) loss of tension related to osteolysis and bone tunnel enlargement, and (4) infection.[51]

The polyester Leeds-Keio artificial ligament was designed to act as a scaffold for neoligamentous ingrowth.[52] The device, having an ultimate load of approximately 2100 N, close to that of the native ACL, performed well early on, but did not have adequate fatigue resistance beyond the first post-operative year.[44, 53] Long term studies indicated fibrous tissue ingrowth was not properly aligned to restore ligament function; therefore, loads continued to be carried by the Leeds-Keio prosthesis, resulting in high rates of rupture.[53-54] The Kennedy LAD was made of polypropylene and designed to support an autogenous graft.[55] Use of polypropylene resulted in reactive synovitis and inflammation accompanied by the proliferation of foreign body giant cells and macrophages.[56]

The Ligament Advanced Reinforcement System (LARS) (Arc-sur-Tille, France) is a newer artificial ligament made of polyethylene terephthalate (PET) with free fibers in the intra-articular section of the device which are arranged in parallel longitudinally, twisted to the left or right depending upon the knee side mimicking the native ACL fiber orientation.[57] The LARS is designed to resist torsional fatigue by reducing shear stresses, which are proportional to the radial distance from the axis of rotation.[57] The radial distance is smaller within free independent fibers than in a construct of fibers forced to twist together as a single larger unit. Additionally, the use of free fibers reduces inter-fiber wear by eliminating the points where fibers cross over and rub against each other.[57] The LARS device has been evaluated in several studies which report high patient satisfaction up to five years after implantation.[58] Mechanical failures of the PET ligament or the fixating screws occur in from 4% to 8% of LARS reconstructions.[58] Other complications that have been observed include superficial wound infection, pain from the screws, and, in one case, synovitis.[58] Despite their long history, prosthetic devices are not widely used currently due to the prevalence of associated mechanical and lack of biocompatibility.[44]

In recent years, interest has grown in tissue-engineered alternatives, which would, in theory, be able to remodel over time as is the case with the native ligament.[44] Tissue engineering of the ligament requires a scaffold which can be seeded with fibroblast or mesenchymal stem cells, and subsequently support neoligamentous growth in an *ex vivo* bioreactor prior to implantation, or *in vivo*, providing function in the knee upon implantation and progressively biodegrading at a rate complementary to tissue ingrowth.[59] Scaffolds have been created from biological polymers such as collagen and silk fibroin as well as biodegradable synthetics such as poly L-lactic acid (PLLA), poly-caprolactone, and polycarbonate.[44, 60-62] Currently,

these types of scaffolds have been shown to be capable of supporting cellular adhesion, growth, and matrix deposition if they are supplied with an appropriate combination of growth factors and mechanical stimulation.[63] However, the precise regimen of cell-specific growth factors, nutrients, metabolites, and the correct physical and dynamic mechanical environment required to grow properly structured ligament tissue have not yet been found. While promising, none of the tissue-engineered constructs have been shown to possess adequate strength or architecture for functional restoration *in vivo*.[59, 63]

The failure modes of previous devices can be addressed within the design control process and risk analysis to improve performance in the next generation ACL prosthesis. Many of the previous devices were susceptible to fatigue and permanent elongation within several years of installation.[44] Damage from fiber abrasion against the bone surface and flexural fatigue have also been observed.[64] Additionally, particulation generated from prosthetics has been known to cause an undesirable immunogenic, inflammatory response.[65-66] New ACL prosthetic devices should be designed with features mitigating each of these undesirable effects.

2.5 Design control process

Design Controls are required by the FDA in the United States and ISO for European regulatory clearance.[67-68] Design Controls are a systematic set of processes and procedures used to ensure that a device is developed and engineered to meet design requirements and is appropriate for its intended use. The system enables designers to iteratively converge upon a suitable design while recognizing and correcting deficiencies in the early stages of the development process. First, user and patient needs are assessed to identify all device requirements and establish the desired features, which may provide a competitive advantage over existing options. When

possible, these needs are compiled and specified in detail becoming the Design Inputs. The acceptable ranges of values for each of the design inputs are stipulated along with appropriate verification and validation tests. The design inputs are reviewed at each phase and are used to guide design efforts. The results of the design efforts at each design phase are the design outputs, which eventually form the specifications for the final device. Verification testing is used to confirm that the Design Outputs comply with the specified design inputs. Validation is the process of objectively establishing that the device specifications conform to the intended use and user needs. Prototypes are repeatedly created, tested, and re-engineered until each design input is verified and the device is validated. [67, 69] A graphical representation of this simplified outline of the development process is the waterfall model shown in Figure 2.2.

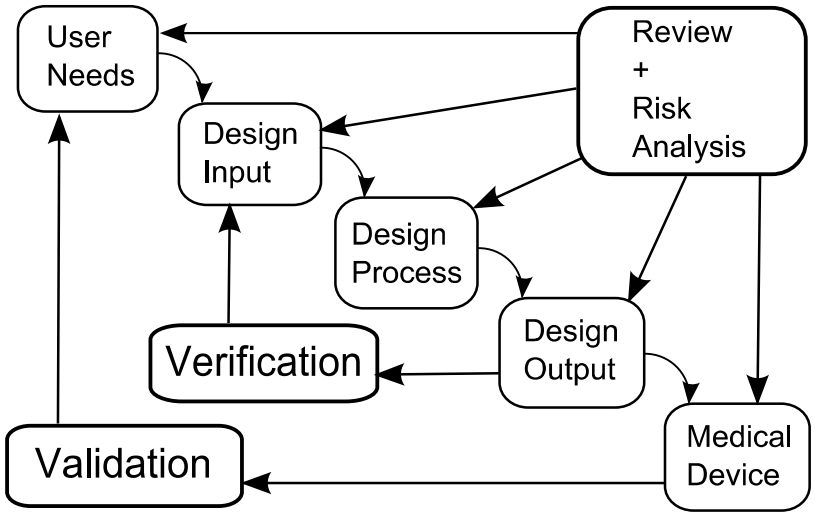

Figure 2.2 Design Control Process. Adapted from FDA guidance document.[69]

The FDA has determined that all intra-articular prosthetic ligament devices pose a significant risk and require premarket approval (PMA) prior to market entry.[70] PMA approval is based upon demonstration of safety and efficacy of the device for its intended use and may require clinical in addition to laboratory data.[70] The regulatory pathway first requires the collection of preclinical data such as results from laboratory

physical, chemical, and mechanical tests as well as animal studies to be included with the Investigational Device Exemption (IDE) application which enables clinical investigation to commence with US patients. The IDE application also requires the submission of an investigational plan for the clinical trial approved by an Institutional Review Board (IRB).

2.6 Design inputs

Based upon our discussions with surgeons in both the United States and France along with a review of the literature, we have devised a set of features defining a prosthetic ACL, which would provide an alternative with advantages over the currently available options. The prosthetic ACL should be implantable in the currently drilled bone tunnel orientations, which have a demonstrated history of functionality and compatibility with the anatomy and physiology of the knee joint. In general, the device should have three sections; the intra-articular ligament-replacing section in the center, with the femoral tunnel segment on one side and the tibial tunnel segment on the other. The intra-articular segment of the device should be similar in size to the native ACL and currently accepted replacements. Autograft and allograft size varies among patients, ranging from 6 to 11 mm in diameter.[71] The ligament-replacing segment should be available in a range of lengths spanning 22 to 41 mm, the reported range of ACL lengths in adults.[72] Each of the tunnel segments can be up to 12 mm in diameter and should have at least 15 mm of length within each bone tunnel.[73-74] The materials used in the device should be biocompatible, free of problems such as unresolved inflammation, immunogenicity, or cytotoxicity.

The ligament-replacing segment mainly acts as a tensile-load bearing structure and should have mechanical properties similar to the natural ligament to restore ACL function in both the immediate and long-term. Relevant mechanical properties include

tensile stiffness, ultimate strength, and ultimate strain which should be within the range of the native ACL and the currently used autografts and allografts. Due to the periodic crimp pattern of the collagen fibrils embedded in the ground substance, the native ACL exhibits a multiphase stiffness profile consisting of a lower stiffness toe region at low levels of strain and a greater linear stiffness beyond that.[4] The presence of a toe region reduces stresses at small strains, and may help prevent fatigue and creep damage.[75-77] The toe region is reported to be present over the first 1 to 3 mm of extension, or anywhere from 2-15% strain.[78-82] Beyond the toe, the linear stiffness of the ACL has been measured between 182 N/mm and 242 N/mm in young donors and as low as 124 N/mm in older donors.[79, 82] Autografts and allografts are several times as stiff as the native ligament. The stiffness of hamstring grafts, for instance, can be as high as 1000 N/mm, which has not been reported to significantly diminish functionality.[83] The ultimate load and strain values should not be less than their native counterparts and preferably greater to provide a safety factor to minimize the risk of re-rupture. The ultimate load of the ACL from young donors has been measured from 1730 N to 2160 N and the ultimate elongation from 6 to 10 mm, or approximately 12-30% strain.[79-80, 82]

In the native ACL, the collagen fascicles, aligned along the ligament axis, resist tensile but not compressive loading which results in a relatively low resistance to bending, folding under its own weight when held from the bottom.[6] The ligament replacement should be designed to sustain repeated bending up to an angle of 80° to 90°.[24] According to the bending formula, EI=MR, the bending stiffness(EI) is the product of the Young's modulus(E) and the second moment of area of the cross-section(I) which is equal to the product of the bending moment(M) and the radius of curvature(R). Specifying that the device should be able to bend up to 90° over the intra-

articular length of the prosthetic while keeping the bending moment below 10 N mm, selected to limit transverse forces on the bones to a small value of less than 0.5 N, the bending stiffness should not exceed 200 N mm^2. The value of 0.5 N was selected as it has been previously used as an allowable tolerance in multiple kinematic studies using robotic/universal force moment sensor testing systems.[84-85]

In addition to having the correct material properties at the time of implantation, the ACL should remain mechanically stable after long-term exposure to cyclic loading under *in vivo* conditions. The device should be engineered with a sufficiently long service life such that the benefits of replacement outweigh the costs. In the best case, the device would provide function for the remaining lifetime of the patient; however, we suspect that if the device could restore function, even for as little as several years, and be easily removed without any complications, it may satisfy demand for a sizeable segment of the market. Active individuals take an average of 6,540 steps per day, or 3,270 per leg.[86] Therefore, the device will undergo approximately 1 million cycles per year of in vivo use with tensile loading to 450 N and bending at angles up to 90°. Over its service life, the device should retain functional stiffness, strength, and length, resisting fatigue from tensile loading and bending, damage from abrasion, and permanent elongation.[70] Furthermore, any wear particulate generated from device abrasion should not cause adverse biological effects such as immunogenic particulation, inflammation, synovitis, and effusion as have been observed with previous prosthetic ligaments.[44]

Each of the tunnel segments should include or be designed to accommodate some type of initial fixator to secure the device within the bone tunnel at the time of installation. The maximum pull-out force for the fixation will need to exceed 450 N, the maximum force incurred over the course of rehabilitation.[78, 87] Initial fixations

currently used with autografts and allografts are not completely rigid, but rather have a stiffness averaging between 40 N/mm and 60 N/mm.[39, 73, 87-89] If the device is to be secured with a suspensory-type fixation only, the stiffness and shape of the device tunnel segment should be such that tunnel motion and widening are not detrimental to function.[90] These effects are generally reduced when an aperture fixation is used, but the current literature has not yet correlated this to improved clinical results.[90-91]

The tunnel segments should possess physical and chemical properties permitting strong long-term incorporation with the bone. Past devices have varied greatly in terms of biologic response and anchorage within the bone tunnel due to differences in material and geometrical design.[92-95] The Gore-Tex and the knitted aspect of the Stryker Dacron prostheses were able to provide strong long-term attachment, supporting infiltration by trabecular bone, intimately surrounded the individual fibers of the device, providing a large surface area for direct contact between the bone and prosthetic.[92-94] Other devices, such as the polypropylene LAD and the Leeds Keio ligament, had more fibrous connective tissue in the intra-osseous segment and less direct bony contact resulting in inferior pull out strength.[92, 94] Studies on medical implant osseointegration and in the area of bone engineering have indicated some requirements for bony ingrowth and incorporation.[96-97] The strength and stiffness of the tunnel segments should be substantial enough to support loading *in vivo* while not being so stiff as to produce stress shielding and resorption of bone near the implant.[96-98] The tunnel segments should have structural and surface properties which permit bony ingrowth and direct apposition of the implant and the bone, allowing transfer of loads across the interface. The device should also have interconnected porosity to allow cell migration, tissue growth, and vascularization within the tunnel segments. Porosity of bone engineering scaffolds can be up to 90% by volume and the optimal pore diameter

for bony ingrowth is reported to be 100-350 microns.[96-97] Hydrophilic materials allow diffusion of nutrients into the device providing an advantage over hydrophobic materials, the presence of which can prevent healthy tissue growth.[96]

A comprehensive chart of design inputs is shown in Table 2.1.

Table 2.1 The Design Inputs for a next generation prosthetic ACL along with associated verification and validation tests.

	Design Input	Requirement	Verification Test	Ref.
1	Biocompatibility	Biocompatible according to ISO 10993 standards for long-term implant devices in direct contact with tissue/bone	Lab and animal testing, histological and immunological assessment, prior clinical usage history of materials used	[70, 99]
2	Stiffness	175-1000 N/mm	Uniaxial tensile test	[78-79, 82, 100-101]
3	Ultimate Load	>1730 N	Uniaxial tensile test	[78, 100-101]
4	Toe-Linear Region Transition Strain	2-15%	Uniaxial tensile test	[78-82]
5	Ultimate Strain	>12%	Uniaxial tensile test	[78-82]
6	Flexibility	Transverse force<0.5 N when bent to 90° over intra-articular length (or Bending Modulus< 200 N mm^2)	Bending test	
7	Dimensions	Length = 60-100 mm (incl. ≥15 mm in each tunnel) Diameter ≤10 mm	Ruler	[4, 73-74, 102]
8	Fatigue	Functional stiffness and ultimate load maintained for >1 Million load cycles from 0 N to 450 N	Fatigue testing	[70]
9	Permanent elongation	<20% elongation after 1 Million cycles from 0 N to 450 N	Measurement of length over course of fatigue testing after preconditioning	[70]
10	Bending Fatigue	Functional stiffness and ultimate load maintained for >1M load cycles from 0° to 80° bending	Bending fatigue test	[70]
11	Abrasion	1) Does not lead to damage and loss of mechanical integrity 2) Size and concentration of particulate matter does not cause problematic immune response *in vivo*	*Ex vivo* mechanical testing, *in vivo* particle migration study, animal study	[70, 103]
12	Prosthetic to bone attachment strength (from fixation device or osseointegration)	>450 N ultimate strength and >40 N/mm stiffness at the time of installation and maintained 1 year *in vivo*	Uniaxial tensile test on cadaver knee (initial) and Animal testing (long-term)	[70, 78, 104]
13	Human factors	Device can be installed by surgeons	User validation test on knee model or cadaver knee with fixation devices	[28]

2.7 Design considerations

A prosthetic is more likely to be adopted if its method of installation is familiar to the surgeon; therefore, it should be similar to a biological graft in that it comprises an intra-articular section which replaces the ligament between sections to be secured within the femoral and tibial tunnels with some mechanism for initial fixation. The device may be produced over a range of lengths and diameters to accommodate variation among patient knee sizes. The selection of materials used to compose the device should be guided by the design input requirements for adequate biocompatibility, elasticity, ultimate strength, and durability or degradability depending upon whether it is to be a frank replacement or a scaffold for tissue engineering. Synthetic or biological polymers and metals might be explored for the application of ligament replacement as many of these materials have adequate tensile strength and good biocompatibility. Hydrogels may also be explored as they are hydrophilic and have the ability to absorb water like the native ligament. Ceramics, though mechanically dissimilar to the ligament, may be included to provide benefits in terms of bioactivity and osteoinduction.[105] Composite structures may enable designers provide advantageous features of several different material types in one device.

The ligament-replacing segment should reproduce the nonlinear tensile response of the native ligament, which is a result of the biochemical composition and structural organization of the tissue. Taking a biomimetic approach, such features of the native ligament can be incorporated into the design of the replacement to provide analogous functional characteristics. As with the native ligament, ropes are composed of many fibers arranged in a regular periodic structure, and can be used to reproduce the non-linear mechanical response of the repeating crimped pattern of the native collagen.[60, 106] Rope structures are also, like the ligament, highly anisotropic and able to sustain

high tensile loads relative to their low flexural rigidity. Common types of rope structures include those formed by parallel alignment, twisting, braiding, knitting, weaving, or some combination thereof. Each of these structures differ with respect to how and to what degree the constituent individual filaments interact with each other which, in turn, affects the mechanical response.[62] These interactions can be extremely complex involving multiple thousands of fibers; however, simplified analytical models of the different structures can be used to describe and predict behavior based upon rope design parameters.[107-110]

The mechanical properties of rope structures can also be modified by altering pattern-specific geometrical and dimensional assembly parameters such as hierarchical arrangement, pitch angle, period length, and so on.[60] Several different types of textile structures can be evaluated and compared first to determine the general effect of the pattern on the static and dynamic mechanical behavior, by comparing strength, stiffness, nonlinearity, as well as resistance to fatigue and permanent elongation. Once a pattern type is selected as the most likely to be able to be adjusted to fit the native ACL stress-strain relation, the pattern-specific parameters can be studied. Sensitivity analyses can be used to identify the critical rope design parameters and indicate how these parameters might be adjusted to create a design that satisfies all the design inputs.

One of the advantages of a prosthetic ACL over the biological grafts is that it enables greater overall control of the design and production, without the limitations imposed by having to adapt to the harvested tissue. Sections of the device may be optimized independently based upon their particular combination of functional demands. The tunnel sections may be designed to provide a physical and chemical environment which can accommodate adequate cellular adhesion, proliferation, and differentiation, factors which determine the overall ability to promote and direct osseointegration.[111]

Relevant design parameters that affect osseointegration of implants include materials, structure, porosity, surface characteristics, biochemical properties, mechanical behavior, and initial fixation. Potential to support bony ingrowth has been demonstrated with a wide range of materials including metals, ceramics, polymers.[111] Morphologically, porous and interconnected network structures with greater surface area are superior to solid structures with smooth surfaces for both bony ingrowth and integration.[111] Increasing porosity can enhance transport of oxygen, nutrients, growth factors, and waste while providing greater space for ingrowth of the new bone, however, it should be noted that increases in porosity come at the expense of mechanical strength and stiffness. The optimum pore size for bone regeneration is between 200 and 400 um, which is large enough to prevent cellular occlusion of the pores, but not so large that cellular adhesion and proliferation are compromised.[111] Bioactive agents, such as calcium phosphates, growth factors, and adhesion-promoting oligopeptides have also been shown to increase the rate of integration and may be included.[105] The mechanical stimuli to which the cells are exposed determines the type of ECM produced.[111] Therefore, some effort should be placed on designing the tunnel segments with adequate mechanics matching and a secure initial fixation.

2.8 Proposed solution

Polyvinyl alcohol (PVA), a hydrophilic polymer, would have several advantageous features as a prospective material for ACL replacement. PVA in the hydrogel form of Salubria® (Salumedica, Atlanta, GA) has demonstrated good biocompatibility and functional capacity in several soft-tissue replacement applications including a nerve sheath, replacement of knee articular cartilage, heart valves, and spinal disks, which, like a prosthetic ACL undergo repeated loading and frictional conditions *in vivo*.[112] Stronger materials such as ultrahigh molecular weight

polyethylene (UHMWPE) may be used to supplement the PVA to provide an increase in the ultimate tensile load or improve creep or fatigue resistance. UHMWPE has demonstrated good biocompatibility and success in hip, knee, ankle, and elbow replacements and surgical sutures for humans and in ligament replacements for dogs.[113-114]

The tunnel segments of the device may be designed as a braided tubular structure providing multiple features suited the demands of short and long term fixation. The fibrous interlocking arrangement of the braid provides interstices akin to porosity thereby allowing ingrowth around the fibers and into the device. The tubular shape can be made such that, when installed in the knee, the outer surface of the device is in contact with the inside bone surface around the entire circumference of the tunnel maximizing the active surface area for bone to graft attachment. Full circumferential graft to tunnel contact is possible with the current graft options if a suspensory type fixation is used, but other fixations such as screws are inserted between the graft and the bone tunnel wall reducing the surface area for contact. By adopting a tubular shape for the tunnel segment a screw may be placed in the open space and used to compress the device against the bone tunnel walls from the inside. The addition of loops adjacent to the extra-articular ends of the tubular sections allows for compatibility with suspensory fixations such as buttons, screws, or staples, which may be used in conjunction with or in lieu of fixation at the aperture. Hydrogels swell as they absorb water, and within the bone tunnels may help reduce tunnel motion by increasing the pressure and tightness of the fit against the bone tunnel wall. Finally, bioactive substances such as calcium phosphates, growth factors, or adhesive peptide sequences may be applied to the surfaces of the fibers or bone chips may be injected into the hollow section to biologically stimulate osseointegration.

2.9 Risk analysis

Risk analysis, the structured process of identifying and evaluating potential problems that may result from usage of the device, is required during the medical device design process for FDA and ISO compliance.[67, 115] Risk analysis tools include fault tree analysis (FTA) and failure mode effects analysis (FMEA). Risk analysis helps product developers to identify potential deficiencies during the design and manufacturing process prior to distribution to avoid costly recalls or product liability issues.

FTA begins by first identifying all the possible failure effects and then listing the potential ways of creating each hazard so they can be designed out. Failure modes can be diagramed on a fault tree connected by logical operators such as “and” and “or” gates and traced back to the contributing basic root causes. Countermeasures can then be applied to avert or mitigate the identified hazards thereby reducing risk. An example risk analysis for a prosthetic ACL is presented in Figure 2.3. The identified possible failure modes include unsatisfactory knee function and immunological rejection that can result from design inadequacies or user errors. Selection of appropriate materials and structural design should be ensured with thorough verification testing of comprehensive design inputs prior to release of the device. Improper installation and patient selection originate from the user and should be examined with validation tests. Training, labeling, product literature, and indications for use can be used to reduce the level of risk arising from surgeon error.

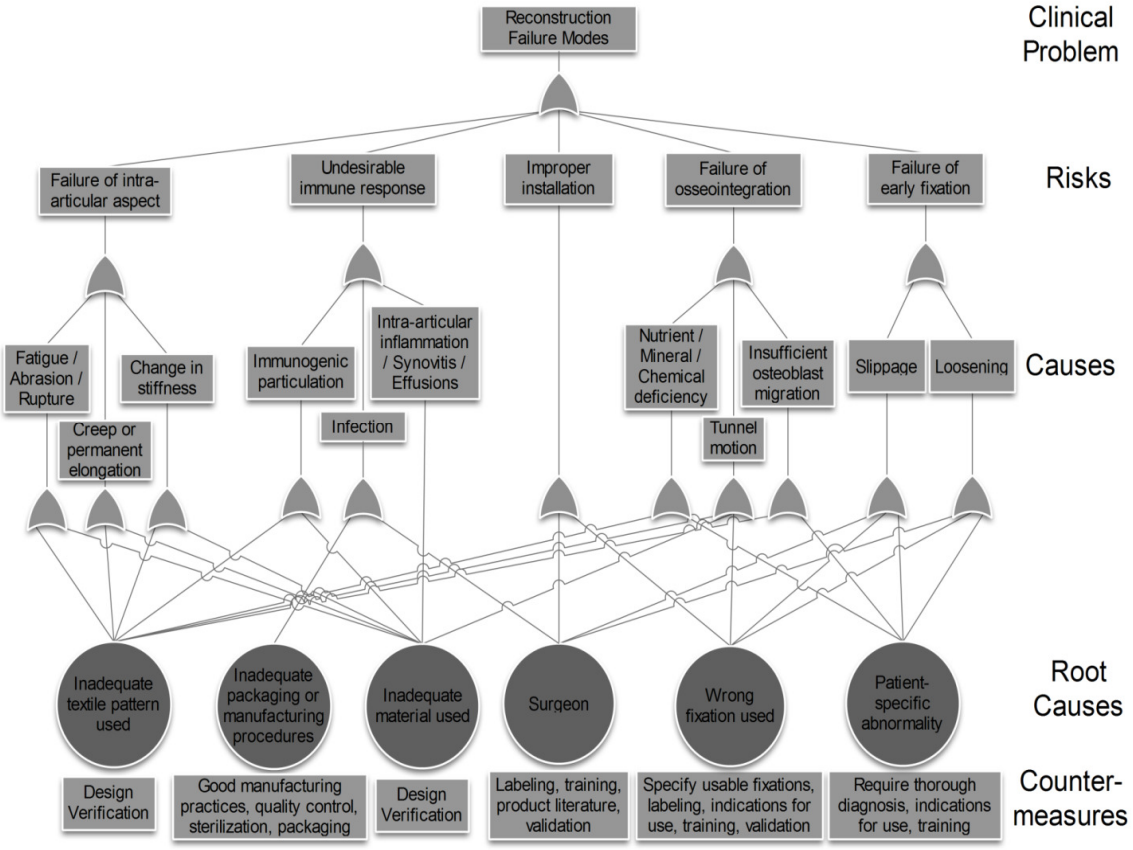

Figure 2.3 A fault tree diagram for a prosthetic ACL. Failure modes are traced back to root causes which can be countered as a part of the design process.

FMEA is a manufacturing tool to assess reliability by analyzing potential failure modes of the device, beginning by identifying potential defects, their effects on safety or performance, and possible solutions. It is often extended to include criticality analysis wherein each hazard is assessed with respect to severity of consequences, probability of occurrence, and probability that it will escape detection before reaching the customer. These factors can then be combined to determine priority ranking so that the hazards which present the greatest danger can be the first to be addressed with corrective actions. One method is to assign numerical ratings to severity, probability, and detection and computing the product to yield a Risk Priority Number (RPN); however, other

methods to determine rank have been proposed and may be superior depending on the application.[116]

2.10 Verification testing

Design Verification is the process of acquiring objective evidence confirming that the design inputs are met. [67] Uniaxial tensile testing may be used to verify most of the mechanical design inputs. Samples can be pulled to failure to test for ultimate strength and ultimate strain or to subfailure loads to test for stiffness focusing on the functional range *in vivo*. Preconditioning may be necessary to assess viscoelastic effects. Testing should be performed with the samples submerged in normal physiological fluid maintained at 37°C unless it is demonstrated that the structural and material properties are not sensitive to these factors.[70] Testing should be performed at several physiologically relevant strain rates to detect any effects on the stress-strain behavior. Mechanical testing of ligaments at strain rates from 0.1%/s up to 100%/s, spanning the range from very slow to very fast motion, has shown that the strain rate does not significantly affect linear stiffness but does affect the strain range of toe region, which reduces as the strain rate increases.[79, 82, 117] Adequate flexibility can be assessed by measuring the resultant transverse force directly when the device is bent to 90° over the intra-articular length.

The functionality of the prosthetic ligament may be compromised by the effects of cyclic loading such as permanent elongation and fatigue. To test for such effects, a periodic load-cycle curve similar to the native ACL such as that described by Shelburne et al.[118] may be imposed over a physiologically relevant force range to simulate the *in vivo* condition. Simpler sinusoidal or triangular waveforms may also be used if any effects of differences in strain rate and strain energy density can be accounted for and it can be demonstrated that the data acquired remains meaningful and relevant to the *in*

vivo response. Over the course of cyclic loading, the stress-strain curves should be measured and recorded, from which the change in stiffness and any progression of permanent elongation can be determined as a function of the number of cycles. For the design to be acceptable, the device should be intact with stiffness and length remaining within functional limits after exposure to the number of cycles expected to occur over its specified service life.

Clinical evidence indicates that cyclic exposure to bending and abrasion are modes of degeneration potentially contributing to device failure. Therefore, in addition to uniaxial tensile static and fatigue testing, cyclic bending and abrasion responses may be used for verification testing of prosthetic knee ligament devices.[70] *Ex vivo* mechanical tests to evaluate bending fatigue would involve subjecting the prosthetic to repeated bending and loading, simulating the *in vivo* condition near the intra-articular bone tunnel exits with regards to graft bending angle combined with tensile loading. The fixations may also be included in these tests.[70] As with the tensile fatigue tests, the device should maintain functional length and stiffness over the duration of the service life. *In vitro* abrasion testing may be included as a part of the bending fatigue test, utilizing cadaver bone or appropriately graded abrasive material to simulate the sections of bone against which the device will rub.[70] The histological and pathological effects of the abraded particulate matter should be evaluated *in vivo* with particle migration and animal studies.[70]

Testing should be conducted to ensure that the functional demands of the bone-to-ligament interface are sufficient through the rehabilitation period and in the long-term thereafter. Ultimate tensile (pull-out) force testing of the initial fixation can be carried out on devices secured in tunnels drilled in cadaver knees. Functional demands of the initial fixation in terms of strength are lower, as early activity will be limited to low loading

during rehabilitation. The long-term demands for strength increase with the level of activity, generally requiring augmentation with bony incorporation.

Biocompatibility testing on representative products made under Good Manufacturing Practices is required to determine if and to what degree the implant might cause any adverse toxicological effects. Standards are available for pyrogenicity testing, hemolytic potential, acute toxicity, intracutaneous irritation, cytotoxicity, and genotoxicity testing to acquire hazard identification information at the pre-clinical stage.[70]

The FDA may also require pathological or mechanical studies of devices implanted in animals. The FDA Guidance Document notes that studies on sheep, goats, and dogs have been previously used and may be appropriate.[70] Animal tests can be used to assess the *in vivo* histological and immunological reaction, material degradation, abrasion, damage, and wear migration, as well as changes in mechanical properties, fixation strength, and longer term bone-to-ligament attachment strength over the course of biological integration *in vivo*.[70]

Clinical trials to demonstrate safety should report evidence of device rupture, joint swelling, tenderness, effusions, synovitis, as well as local or systemic infection. [70] Efficacy and function can be directly assessed using the anterior drawer test, Lachman test, and pivot shift test and the device itself can be examined using MRI. Clinical outcome can be measured in terms of the Lysholm knee scoring scale, Tegner activity scores, or IKDC scores.[70]

2.11 Discussion

A prosthetic ACL would solve many problems associated with the existing options for ACL replacement, such as donor site morbidity and the necessity of the harvest operation in the case of autografts as well as lack of availability and disease

transmission risk associated with allografts. Synthetic ACL prostheses have been withdrawn from the US market since the early 1990s due to lack of biocompatibility and recurring mechanical failures; however, new advances in biomaterials, surgical techniques, biomechanics, and tissue engineering provide an opportunity to design a new generation of prosthetic ACL replacements with the goal of improving biocompatibility, mechanical behavior, fixation, and bony integration. The development of prosthetic ACL device, installable with current surgical techniques, with good biocompatibility, mechanical behavior similar to the native ACL, and the ability to provide function over millions of cycles would be a significant advance in the field of knee surgery. The availability of an off-the-shelf alternative to autografts and allografts would reduce operation times and costs, accelerate recovery, and improve outcomes, providing clear advantages for both patients and surgeons.

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CHAPTER 3 Mechanical Evaluation of Materials and Rope Structures for an Anterior Cruciate Ligament Prosthesis

3.1 Introduction

The ACL is a tensile load bearing structure functioning as a restraint to excessive anterior translation of the tibia relative to the femur, maintaining proper knee orientation and stability.[1-2] Tearing or rupture of the anterior cruciate ligament (ACL) is a relatively common sports-related injury with up to 100,000 cases each year in the United States.[3] Due to the poor blood supply of the ACL in the adult, it does not heal on its own nor respond well to primary repair; therefore, reconstruction with an autograft or allograft is the currently prescribed method of treatment.[4]

The usage of autografts is associated with good results; however, drawbacks such as residual donor site morbidity, longer recovery times, and the requirement of the additional harvest operation would make a prosthetic with off-the-shelf availability an attractive alternative for many surgeons and patients.[5] Beginning in the 1970s, a series of prosthetics were developed from a wide range of polymeric materials; however, due to high rates of mechanical failure and immunogenic particulation, the field has turned away from these types of devices.[6] As surgical techniques and tools have since improved and a wider range of novel biomaterials have become available, the question of whether a functional prosthetic can be developed is worth exploring again.

To adequately restore function, a prosthetic device should possess mechanical properties within the range of the native ACL or the currently accepted replacements. As a function of the composition and orientation of the tissue, the native ligament exhibits a nonlinear elastic response in which at low levels of strain, there is a low stiffness toe regime, and at greater levels of strain, a higher stiffness linear regime.[7]

The strength and linear stiffness derive from collagen in the form of fibrous bands arranged axially in parallel. A periodic crimped or wavy pattern in the collagen accounts for the observed toe region.[7] The collagen is embedded in a hydrophilic ground substance consisting of proteoglycans, elastin, and water.[7] The mechanical design inputs for the ligament-replacing section of a prosthetic ACL replacement are outlined in Table 3.1.

Table 3.1 Mechanical design inputs for a prosthetic ACL.

Design Input	Value	Verification Test	Ref.
Stiffness	35-400 N/%	Uniaxial tensile test	[8-11]
Ultimate Load	>1730 N	Uniaxial tensile test	[8-9, 11-12]
Toe-Linear Region Transition Strain	2-15%	Uniaxial tensile test	[4, 9, 13-16]
Ultimate Strain	>12%	Uniaxial tensile test	[4, 9, 13-16]
Fatigue	Functional stiffness and ultimate load maintained for >1M load cycles from 0N to 450 N	Fatigue testing	[17]
Permanent elongation	<20% permanent elongation after 1M cycles from 0N to 450N	Measurement of length during of fatigue testing	[17]
Diameter	<10 mm	Ruler	[2, 18]

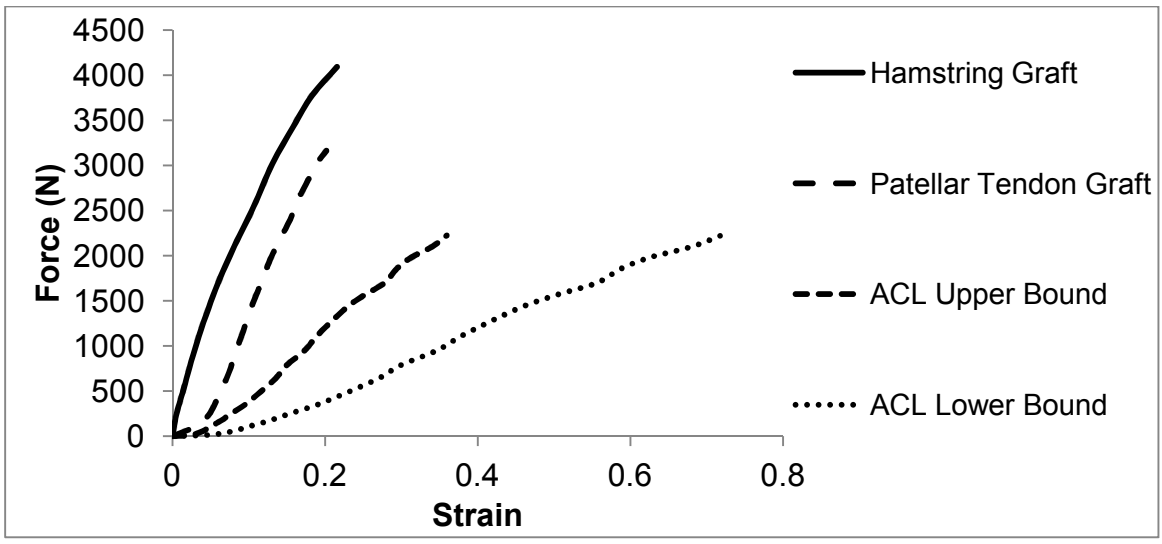

Figure 3.1 Force vs. strain relationship for the native ligament shown alongside patellar tendon graft and double-looped hamstring graft.[2, 4, 9, 13, 15, 19]

3.2 Methods

3.2.1 Materials selection

Polyvinyl alcohol (PVA) is a promising biomaterial with excellent biocompatibility currently showing potential in several soft-tissue replacement applications such as knee cartilage and vein valve repair.[20-21] PVA is hydrophilic, forming a hydrogel when in contact with water. It can also be manufactured in a fibrous or filamentous format. We hypothesize that PVA arranged in a periodic rope pattern can provide an acceptable mechanical response for ACL replacement. A high-strength material, such as ultrahigh molecular weight polyethylene (UHMWPE) may also be added to provide additional support and a safety factor in terms of ultimate load. UHMWPE has been implanted for many years as a component of hip, spine, and knee replacements for humans and in ligament replacements for dogs with a long record of good biocompatibility.[22-23]

3.2.2 Design considerations and process overview

The nonlinear tensile behavior of the native ligament, derived from the periodic structure of the collagen fibers, is not likely to be reproduced by a solid bulk material or straight fibers arranged in parallel. Biomimetic principles suggest that rope structures, being periodic, wavy, and fibrous, may be better suited for a ligament replacement. The approach taken in this investigation is as follows. In Study 1, PVA and UHMWPE were mechanically assessed as prospective materials for ACL replacement with the objective of determining the quantities of each material required to provide adequate strength and stiffness while remaining within dimensional constraints. Then, in Study 2, several basic types of structures were compared experimentally to determine the effect of rope pattern on tensile behavior, and from that select the pattern with the most ligament-like response. Next, in Study 3, pattern-specific geometrical parameters were analytically and experimentally studied to converge upon a final design to adequately match the static response. Finally, in Study 4, the long-term behavior of the final design is tested by applying repeated loading simulating the *in vivo* condition and observing the progression of fatigue and elongation.

3.2.3 Rope analysis

Filaments are arranged in rope structures to force them to act as a single unit and increase tensile strength. Methods to organize filamentous materials into rope structures include twisting, braiding, knitting, and weaving. The mechanical response of each of these structures is dependent upon the material composition as well as structure-specific geometrical assembly parameters. Furthermore, hierarchical arrangements can be imposed with different patterns at each level or layer. A brief summary of some analytical methods to relate structural parameters to mechanics is provided below.

3.2.3.1 Twisted structures

Gegauff was the first to analyze twisted yarn structures and derive a simple relationship between the twisting angle and the tensile modulus.[24] In this model, the yarn is idealized as a series of concentric cylindrical layers each consisting of helically wound filaments. Focusing on one layer at a radial position, r, let the helix angle at that layer be denoted by θ and the length along the yarn axis for one complete turn be denoted by h. The length along the filament axis for one complete turn is denoted by l. δh and δl represent elongations along the yarn axis and filament axis respectively.

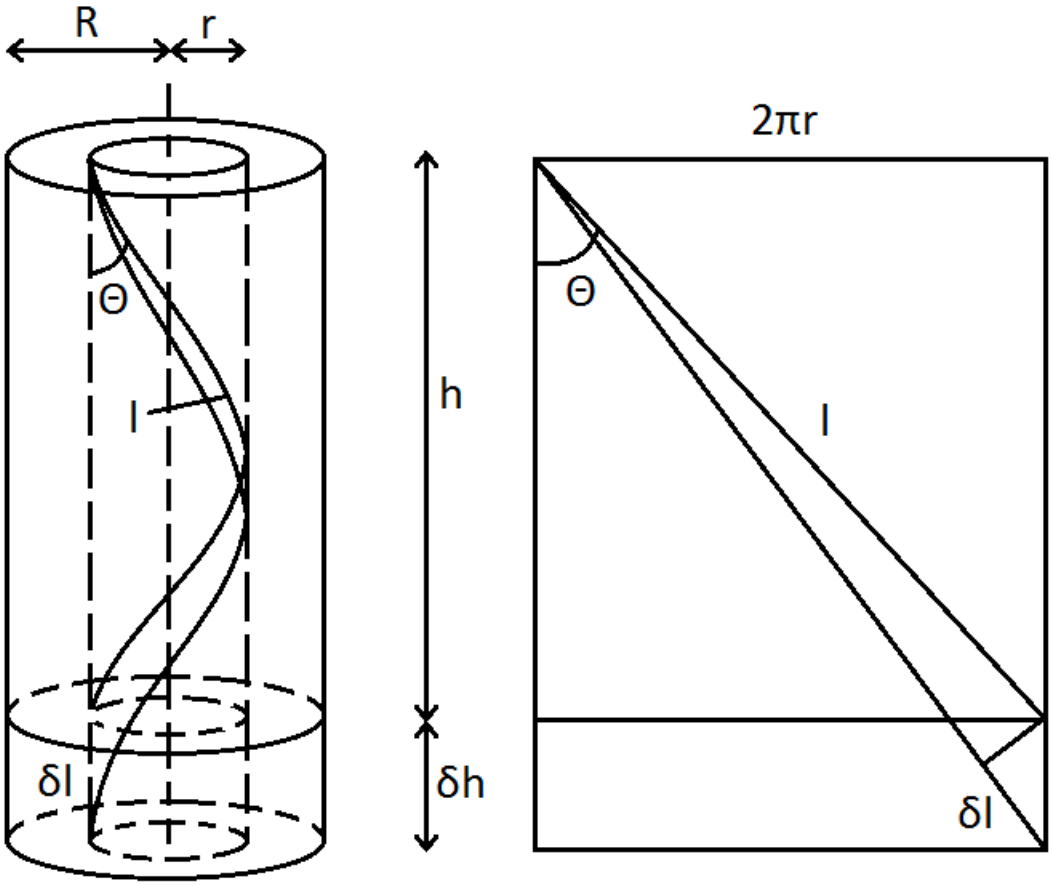

Figure 3.2 Ideal geometry of a twisted yarn (left) and flattened projection of one filament over one helical turn (right).[25]

The strain in the yarn, ε_y, and the strain in each filament in the layer, ε_f, are defined as follows:

$$\varepsilon_y = \delta h/h,$$

$$\varepsilon_f = \delta l/l.$$

Furthermore, we can see that,

$$h = l\cos\theta,$$

and

$$\delta h \approx \delta l/\cos\theta,$$

assuming the change in θ is small.

Therefore, by substitution, the relationship between yarn and filament strain is,

$$\varepsilon_f = \varepsilon_y \cos^2\theta.$$

If F_y is the component of force in the direction of the yarn axis in each filament in the layer, the force in the filament along the filament axis is $F_f = F_y/\cos\theta$. Additionally, the area of the cross-section perpendicular to the axis of the filament, A_f, can be expressed as a function of the area of the cross-section perpendicular to the yarn axis, A_y, as, $A_f = A_y \cos\theta$. The stress in each filament of each layer, $\sigma_f = F_f/A_f$, can therefore also be calculated in terms of the equivalent stress in the layer, $\sigma_y = F_y/A_y$. At each layer the stress in the filaments can be expressed as,

$$\sigma_f = \sigma_y/\cos^2\theta.$$

And since the modulus of the rope is $E_y = \sigma_y / \varepsilon_y$, and the modulus of the filament is $E_f = \sigma_f / \varepsilon_f$,at each layer, they can be related for each layer as,

$$E_y = E_f \cos^4 \theta.$$

Now, looking at the whole rope as a series of concentric layers, the average value of $\cos^4\theta$ is $\cos^2\alpha$ where α is the helix angle for the outermost layer. Therefore,

$$E_y = E_f \cos^2 \alpha.$$

Subsequent experimental studies have shown that the reduction in modulus resulting from the twisting of filaments into yarns is greater than this simple model predicts and more complicated models have been developed. White et al.[26] derive the relationship as,

$$E_y = E_f \left(\frac{1}{4} + \frac{9}{4}T + \frac{3T}{(1-T)} \ln T^{1/2}\right),$$

where $T = \cos^2\alpha$.

Another model derived by Rao et al.[25] takes into account the shear modulus of the filament yielding,

$$E_y = E_f \left[\frac{3T+1}{2dT} + \frac{(1+d)^2}{d^3 \tan^2 \alpha} \ln \frac{(1-d)T+d}{T}\right],$$

where d is the ratio of the longitudinal modulus to the shear modulus.

It is important to note that these models neglect any radial contraction of the rope as it is strained in the axial direction.

3.2.3.2 4-strand square braided structures

Braiding is broadly defined as interweaving three or more lengths of material into a diagonal overlapping pattern. A square braid is composed of four subunits, arranged in a way such that one pair zigzags across itself in one plane and the other pair does the

same in the perpendicular plane. A schematic of the centerline of the structure is shown below.

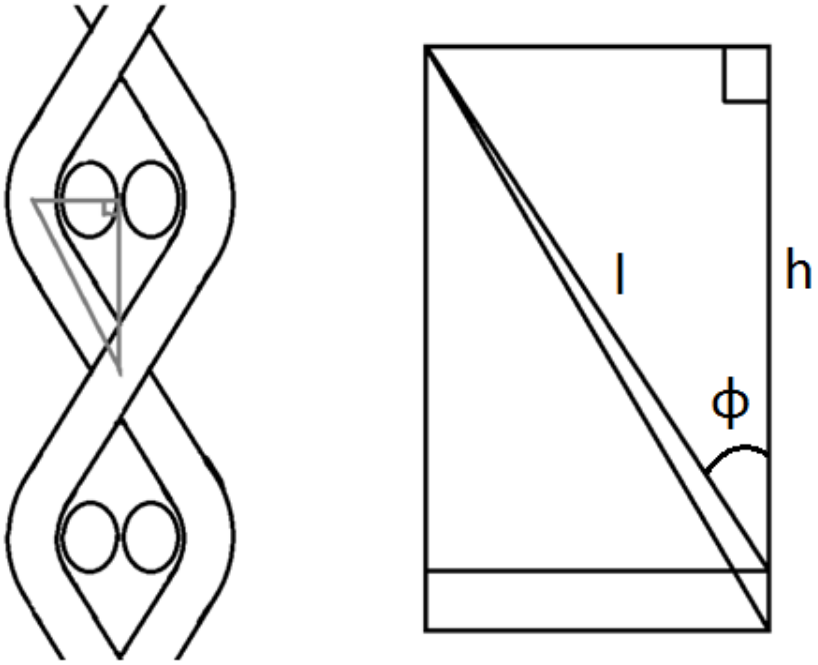

Figure 3.3 Idealized geometry of a 4-strand square braid (left) and magnification of one square braid unit cell (right).

Approximating a unit cell as a right triangle, the stiffness of the overall structure can be predicted as a function of the material properties of the constituents. The angle between the component and the braid axis is denoted as φ, the axial length as h, and the component length as l. With an analysis parallel to the single layer of the twisted rope described above, it can be shown that

$$E_y = E_c \cos^4 \phi \ ,$$

where E_y is the modulus of the yarn, and E_c is the modulus of the component. This relationship can be used directly to estimate yarn modulus. As in the twisted models described above, radial contraction is neglected.

3.2.3.3 Hollow braided structures

Another type of braided structure is the circular or hollow braid which forms an open cylinder with a diamond lattice pattern. The mechanics of these types of structures is described by Hopper and Grant.[27] In the simple case, in which there is nothing inside of the circular braid, there are two modes of configuration, unjammed and jammed, which determine the mechanical response. As axial loads are first applied to these braids, the diamond extends along the axial direction while simultaneously contracting in the circumferential direction. Jamming occurs when, upon axial elongation, the space between each of the components in the circumferential direction collapses to zero. In the unjammed state, as axial strain is imposed, there is no strain incurred in each of the braid components, but rather the axial strain is only a result of the deformation of the diamond lattice. The resistance to extension is due only to negligible frictional effects and not the properties of the components. In the jammed state, circumferential contraction is restricted, and therefore as axial strain increases, strain is also incurred in the components.

The locking angle, θ_L, can be calculated from the following relationship,

$$\sin 2\theta_L = \frac{w}{X_0} \sin \theta_0,$$

where w is the width of each component, X_0 is the initial lateral dimension of the diamond lattice, and θ_0 is the initial angle between the braid axis and the components.

In the unjammed state, the axial force generated with axial strain is very low as there is very little resistance to deformation of the diamond lattice. Conversely, upon transition to the jammed state, the stiffness rapidly increases as axial strain is resisted by tension and strain in each of the braid components. The total axial tension in the braid can be determined as a function of the braid and yarn properties as

$$T_b = NT_{comp} \cos\theta_L,$$

where N is the number of components, and T_b and T_{comp} are the tension in the braid and each component respectively. T_{comp} can be determined as a function of the strain in each component, ε_{comp}, given the material stress-strain relation. The component strain can be calculated from the braid strain, ε_b, as

$$\varepsilon_{comp} = \varepsilon_b \cos^2\theta.$$

The addition of an elastic core in the center of the hollow braid is slightly more complex as there are additional modes. In the first mode, the hollow aspect is unjammed and is not in contact with the central core. As extension occurs in Mode I, the diamond lattice of the hollow aspect deforms without strain being incurred in the components. The core, however, does bear load and strain, while also contracting laterally due to the Poisson's effect. The Mode I force is only dependent upon the core and can be expressed as,

$$F = k_c \varepsilon_z L_0 \ ,$$

where k_c is the stiffness of the core, ε_z is the axial strain, and L_0 is the initial length. Mode I type behavior occurs under the condition that the inner radius of the hollow aspect is greater than the radius of the core. This relationship can be expressed as,

$$\sqrt{1 - \frac{2\varepsilon_z + \varepsilon_z^2}{\tan^2\theta_0}} - \underline{t} > \underline{r_{c0}}(1 - \nu\varepsilon_z)$$

where θ_0 is the initial helix angle, $\underline{t}$ and $\underline{r_{c0}}$ are the thickness and initial core radius of the hollow aspect relative to the width of the diamond lattice respectively, and v is the Poisson's ratio of the core.

In Mode II, the hollow braid remains unjammed, but has come into contact with the elastic core. The resistance of the elastic core to compression results in tension in each of the hollow braid components. Therefore, the force along the braid axis of the construct consists of contributions from both the core and hollow aspect. In this mode, the inward and outward forces between the core and hollow aspect must be balanced to solve for the radius and helix angle. To do this we set the inner braid radius equal to the core radius obtaining,

$$\sqrt{\frac{(1+\varepsilon_y)^2}{\sin^2\theta_0}-\frac{(1+\varepsilon_z)^2}{\tan^2\theta_0}}-\underline{t}=\underline{r_{c0}}(1-\varepsilon_r)\ ,$$

where ε_y is the hollow braid component strain and ε_r is the core radial strain,

$$\varepsilon_r=-\frac{(1+\nu)(1-2\nu)\varphi_c\underline{r_{c0}}^2\sin^2\theta\zeta\varepsilon_y}{2M\underline{r_b}^2\cos\theta}-\nu\varepsilon_z\ ,$$

where ϕ_c is the core packing factor, ζ is a non-linear correction factor, and $\underline{r_b}$ is the non-dimensional braid radius. Additionally,

$$M=\frac{\varphi_c k_c L_0}{N\varphi_y k_y L_{y0}}\ ,$$

where ϕ_y is the braid component packing factor, k_y is the component axial stiffness, and L_{y0} is the component initial length.

In Mode III, the hollow aspect of the braid becomes jammed while remaining in contact with core. When the core laterally constricts to the point it is no longer in contact with in jammed hollow aspect, this is Mode IV. In each of these modes, the angle can be calculated as,

$$\theta_L=\sin^{-1}\left(\frac{\underline{w}\tan\theta_0}{2(1+\varepsilon_z)}\right),$$

where $\underline{w}$ is the non-dimensional width of each hollow aspect component. The non-dimensional braid radius can be calculated as,

$$\underline{r_b} = \frac{1}{\sqrt{\left(\frac{2}{\underline{w}}\right)^2 - \left(\frac{\tan\theta_0}{1+\varepsilon_z}\right)^2}} .$$

In general, the yarn strain is

$$\varepsilon_y = \frac{\cos\theta_0}{\cos\theta}(1+\varepsilon_z) - 1 .$$

Furthermore, the total axial force can be calculated as,

$$T = N\varphi_y k_y L_{y0}\left\{\zeta\varepsilon_y\cos\theta + M\left[\frac{(1-\nu)\varepsilon_z + 2\nu\varepsilon_r}{(1+\nu)(1-2\nu)}\right]\right\} .$$

The complete derivation of these relationships for hollow braided ropes is found in the paper by Hopper and Grant.[27]

3.2.4 Rope preparation

Filaments of PVA were fine and difficult to manage individually. Therefore, fifteen monofilaments of PVA were twisted together to form a thread and fifteen of these threads were again twisted together to make one cord. Each cord was approximately two millimeters in diameter. UHMWPE threads were 4-component braided structures approximately half a millimeter in diameter. Each UHMWPE thread braid component consisted of many very fine filaments in parallel.

For Study 1, the PVA cord and UHMWPE thread were first tested on their own to determine how much of each material would be needed to provide stiffness and strength within the range of the native ACL or currently accepted grafts while remaining within size constraints. Subsequently, twisted ropes consisting of 16 PVA cords were tested and compared to the same supplemented with 12 UHMWPE threads to determine if

there were any significant advantages with the addition of the UHMWPE. The 16 PVA twisted structures with or without the UHMWPE were approximately 8 mm in diameter, an appropriate size for an ACL replacing device.[2, 18, 28]

To examine the effect of rope pattern on the static tensile behavior of the device in Study 2, samples were created with the following pattern types: (1) twisted, (2) 4-strand square braided, and (3) hollow braided with elastic core. Each of the types contained a controlled quantity of 16 PVA cords and 12 UHMWPE threads, such that rope pattern would be the only variation. For the twisted samples the UHMWPE threads were aligned in parallel and utilized as a single unit and along with each of the PVA cords were twisted around the longitudinal axis of the sample. For the 4-strand square braided samples, three of the strands were parallel bundles each consisting of 4 PVA cords and the fourth strand was a bundle of 4 PVA cords together with 12 UHMWPE threads. Finally for the hollow braid, 16 PVA cords were aligned in parallel forming the elastic core and surrounded with tubular diamond braid of 12 UHMWPE threads.

Study 3 focused on the hollow braid design parameters. To study the effect of core size on the mechanical response of hollow braided structures, samples with 8, 12, and 16 PVA cords in the core surrounded by 12 UHMWPE threads. The respective diameters of these constructs were 5.5 mm, 7 mm, and 8 mm respectively. Then, to test the effect of the helix angle, samples with 16 PVA cords in the core and 12 UHMWPE threads in the braid were created over a range of helix angles. The long-term performance evaluation, Study 4, was carried out on hollow braided structures with 8 PVA cords as the core surrounded by 12 UHMWPE threads.

3.2.5 Braid computational analysis

Using the analytical model for the hollow braid with an elastic core as described by Hopper and Grant,[27] a MATLAB function was written to calculate the theoretical force versus strain relationship as a function of PVA cord and UHMWPE thread quantities, mechanical properties, and braid geometrical parameters such as core diameter and lattice dimensions.

3.2.6 Static tensile testing

Samples were submerged in water at room temperature for 24 hours, then removed from the water and tested wet on an Instron 5966 materials testing system (MTS). For pull-to-failure tests, carried out to determine ultimate strength, capstan fixations with a diameter of 7 cm were used to secure the samples from each end. The long ends of each sample were wrapped around each capstan three times and tied to the frame and crossbar on the materials testing machine. Capstans were used because they provided a holding force greater than the ultimate load of the samples and increased the likelihood that rupture occurred in the body of the sample due to the tensile force. Other systems such as gripping with clamps or tying the sample around bars had greater amounts of slippage and were prone to cutting the samples or inducing abnormal stress concentrations leading to premature failure at the grip to sample interface. For sub-failure tensile testing, focusing on the physiologically relevant force range for both normal and strenuous activity up to 700 N, large wedge clamps were used as they adequately gripped the samples from each end without causing slippage and damage.[9, 29]

Samples were pre-stretched for 20 cycles between 0 and 700 N before being pulled for testing at a rate of 2% per second, corresponding to a medium to slower motion *in vivo*.[30-31] The rate was fast enough to ensure negligible drying over the

duration of the test. To avoid distortion of results introduced by the irregularities of grips and clamping system, strain was independently measured and calculated from a video recording of the motion of black markers on the midsubstance of the sample and subsequently synchronized with force measurement data from the MTS. The frame grabbing system consisted of an AVT Pike camera placed approximately 1.5 meters away from the test sample with a data acquisition rate of 2 images per second. From the video, recorded to a PC, each frame in sequence was then analyzed with a custom marker pixel tracking software application to determine the strain. The resolution of the system was approximately 100 μm, accurate to 0.2% strain. For each sample type and static test a sample size of n≥5 was used.

3.2.7 Long-term mechanical testing

A custom testing system was assembled to apply long-term cyclic loading to rope samples. After preloading to 500 N, the system operated in force control mode in the normal non-strenuous activity force range between 50 N and 450 N up to 1 million cycles at a frequency of 1 Hz, while constantly recording force and displacement data.[9] The samples (n=4) were clamped at each end and completely submerged within a cylindrical chamber filled with water at room temperature for the duration of the investigation. Force and displacement data was used to record the progression of fatigue and elongation as well as changes in the static response. Gross observation of the sample was used to identify wear and damage. Testing was extended to determine number of cycles to failure for one of the samples.

3.3 Results

3.3.1 Study 1: Material evaluation

Tests on single PVA cords indicate an average stiffness slightly greater than 2 N/% and an ultimate load close to than 140 N. Therefore, it was predicted that a minimum of 15 to 20 PVA cords in parallel would be required to provide the minimal stiffness requirement of 35 N/% if only PVA were to be used. UHMWPE threads had a much greater stiffness close to 100 N/% and a greater ultimate load of 375 N despite having only a small fraction of cross-sectional area of the PVA. Six UHMWPE threads together would be adequate to provide an ultimate load exceeding 2160 N, the average ultimate load of the ACL in the young adult.[13]

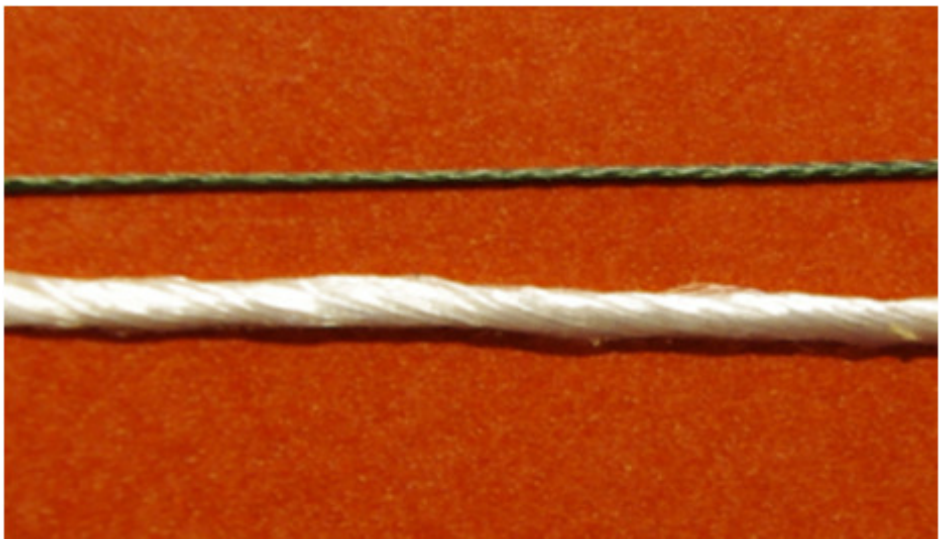

Figure 3.4 One UHMWPE thread (top) and one PVA cord (bottom)

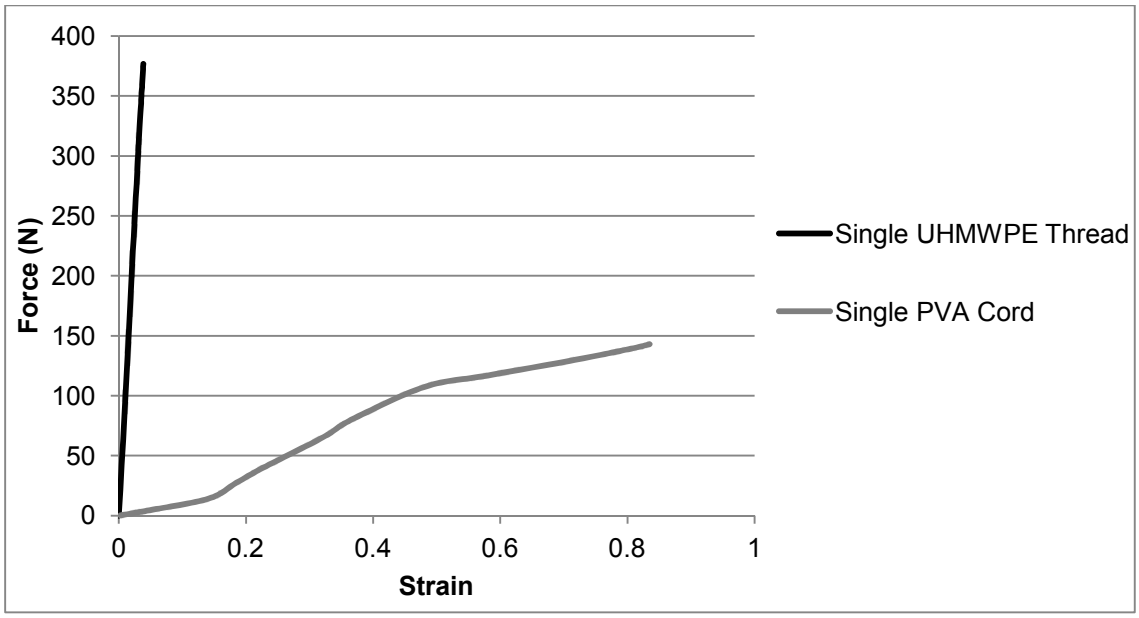

Figure 3.5 Force versus strain relationship for one saturated PVA cord and one saturated UHMWPE thread.

Twisted bundles of 16 PVA cords, which were 8 mm in diameter, similar in size to an average hamstring graft,[18] were found to have a stiffness close to the lower bound for acceptability and strength slightly inferior to the native ACL.[13] Increasing the number of PVA cords to 22, the maximum allowable before exceeding our size constraints, provided an ultimate load equivalent to the average ACL, however did not provide any safety factor beyond that. Addition of 12 UHMWPE threads twisted together with 16 PVA cords provided an ultimate load twice that of the native ACL without significantly increasing the diameter; however, this arrangement also resulted in a very high stiffness when the response was dominated by the UHMWPE. The desirability of a safety factor for ultimate load supported the conclusion that the inclusion of 12 UHMWPE threads would be advantageous, but raised the question of whether it would be possible to keep that strength while reducing stiffness closer to the level of native ACL to better limit shock during *in vivo* loading.

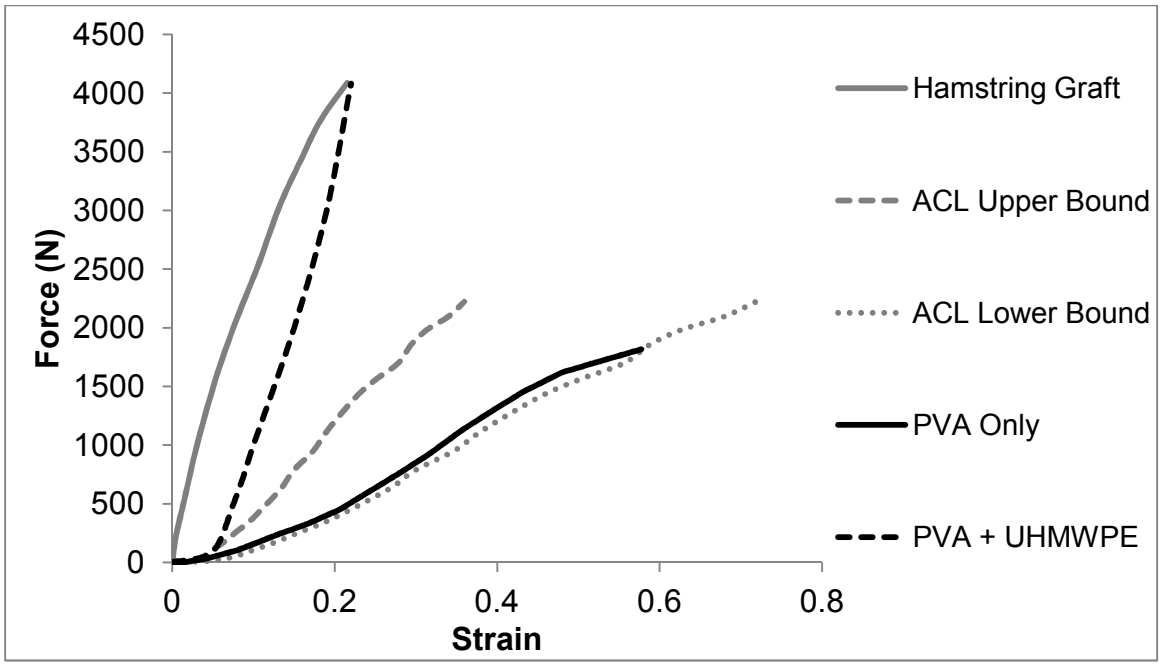

Figure 3.6 Force versus strain relationships for a twisted bundle of 16 PVA cords, and the same twisted along with 12 UHMWPE threads compared with the native ACL and hamstring autograft.[2, 13, 19]

The results of Study 1 demonstrated that a quantity of 15 to 22 PVA cords provided good stiffness for ACL replacement, however, using more than 16 PVA cords resulted in a diameter greater than the ideal. Additionally, it was found that much greater strength would be provided with the addition of 12 UHMWPE threads, but that the stiffness of the UHMWPE far exceeded that of the ACL. It was hypothesized that a biomimetic composite structure using PVA cords and UHMWPE threads arranged with some type of periodic rope pattern could result in a hybridization of the mechanical properties of two materials resulting in the desired ligament-like response.

3.3.2 Study 2: Effect of rope pattern

To evaluate how the rope pattern affects the static tensile behavior, twisted, 4-strand square braided, and hollow braided samples were created for mechanical comparison, each composed of a controlled quantity of 16 PVA cords and 12 UHMWPE threads. These patterns were evaluated based upon the tensile response in the

physiologically relevant force range from 0 N to 700 N, and compared to the native ACL and currently used autografts. Twisted and 4-strand square braided samples exhibited a very similar behavior characterized by a well-defined low stiffness PVA-dominated regime at low strain and a very high stiffness UHMWPE dominated regime at higher strains. The transition in both of these types of patterns occurred relatively rapidly, over a three percent change in strain beyond which the stiffness of the UHMWPE-dominated regime was close to three times as stiff as the native ACL. Alternatively, the hollow braided samples had a much more gradual transition from low to high stiffness spanning across approximately 10 percent strain before being completely dominated by the UHMWPE. Notably, the stiffness over the course of the transition approached that of the normal young ACL.

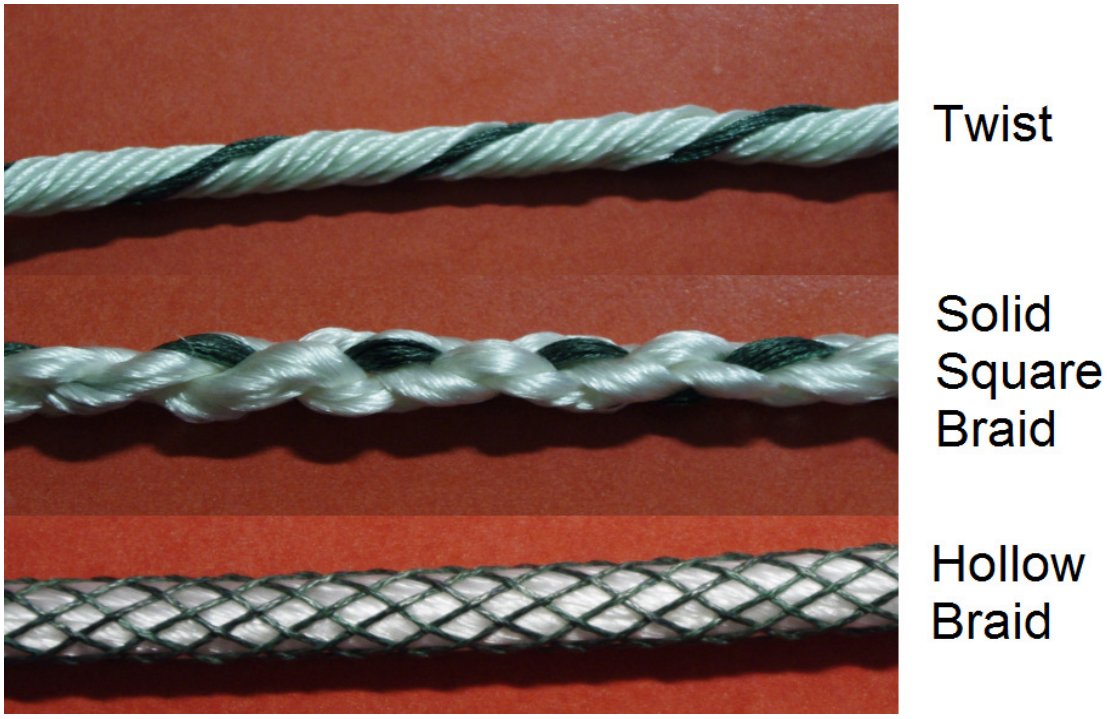

Figure 3.7 Twisted, 4-strand square square braided, and hollow braided samples.

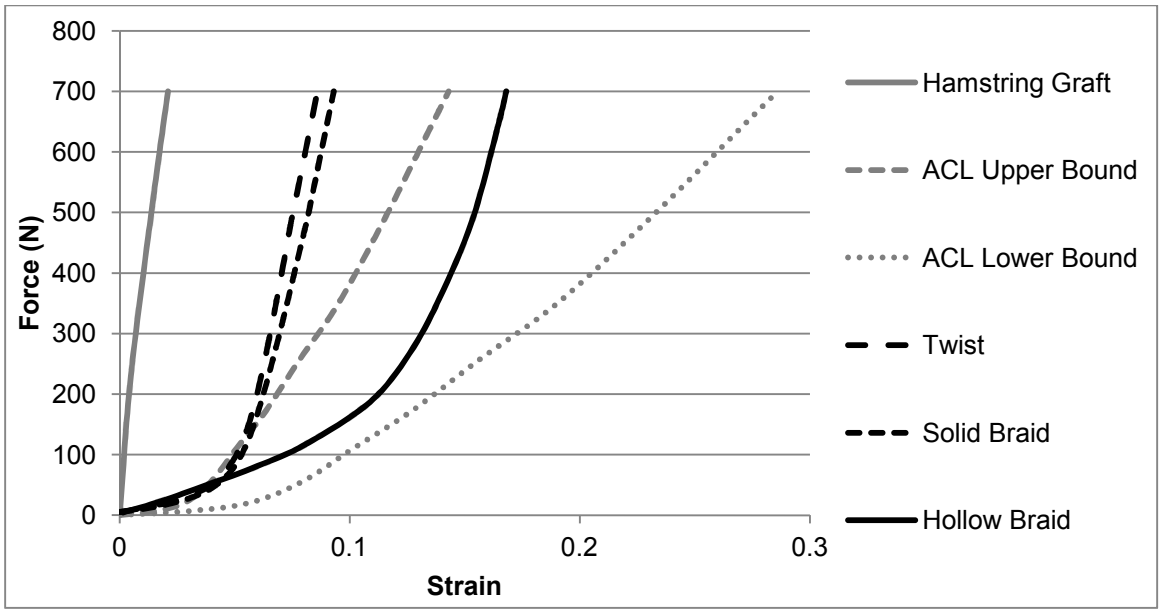

Figure 3.8 Force versus strain relationship for twisted, 4-strand square braided, and hollow braided specimens compared to the native ACL and hamstring autograft.[2, 13, 19]

The results of Study 2 established the hollow braided structure as providing the most ligament-like mechanical response and led to the question of how the geometrical and compositional parameters of hollow braided structures could be altered to further diminish the contribution of the UHMWPE in the functional strain range and achieve stiffness nearer to that of the native ACL.

3.3.3 Study 3: Effect of hollow braid parameters

Proceeding with hollow braided structures, the inclusion of 12 UHMWPE threads was specified as that was the minimum amount capable of providing an ultimate strength double that of the native ACL. Other parameters left to adjust included the number of PVA cords in the core and the helix angle at which the UHMWPE threads were to be laid around the core.

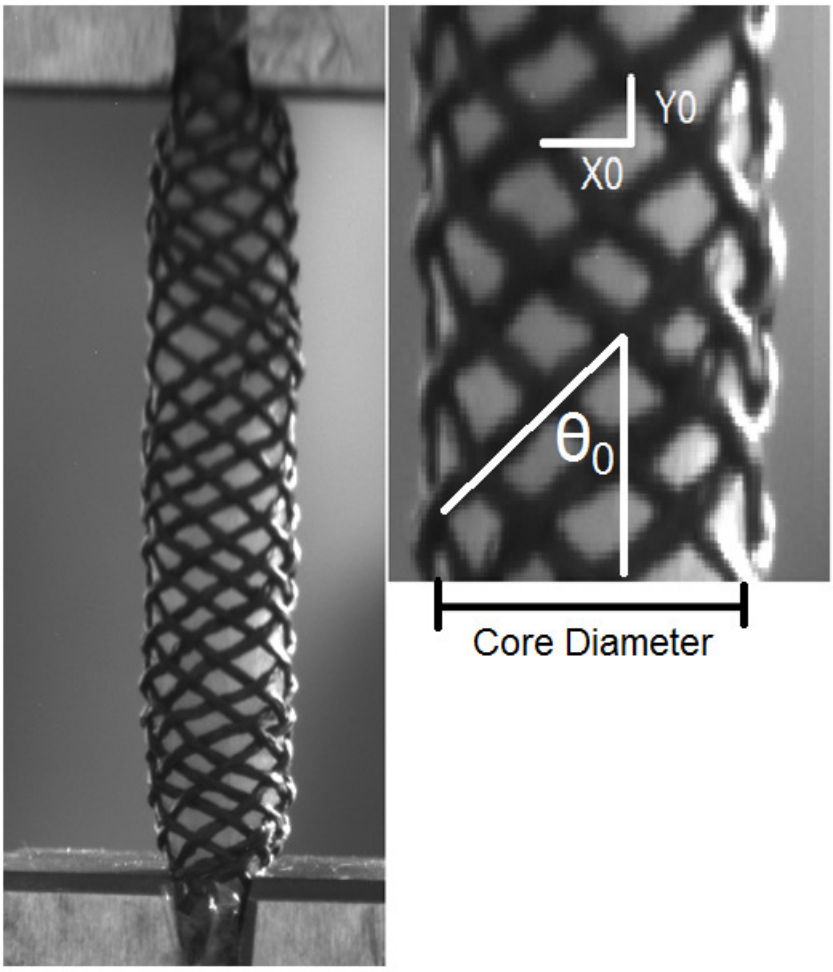

Figure 3.9 Hollow braid geometrical parameters include the helix angle (θ_0), circumferential braid dimension (X0), longitudinal braid dimension (Y0), and core diameter.

The effect of the number of PVA cords in the core was studied first. Hollow braids with 12 UHMWPE threads outside and cores composed of 8, 12, and 16 PVA cords in parallel, with diameters of 5.5 mm, 7 mm, and 8 mm, respectively, were tested and compared to the native ACL over the physiologically relevant force range from 0 N to 700 N. The force versus strain curve (Figure 3.10) shows that increasing the number of PVA cords had the effects of increasing the stiffness of the toe region in direct proportion to the number of PVA cords and smoothing the transition from lower to higher stiffness resulting in a more ligament-like stiffness overall. These finding suggested that

more PVA in the core would be superior, however, increasing the number of cords beyond 16 would result in a diameter larger than the currently used grafts.[18] To avoid any size issues, 16 PVA cords was selected as the ideal quantity for the core.

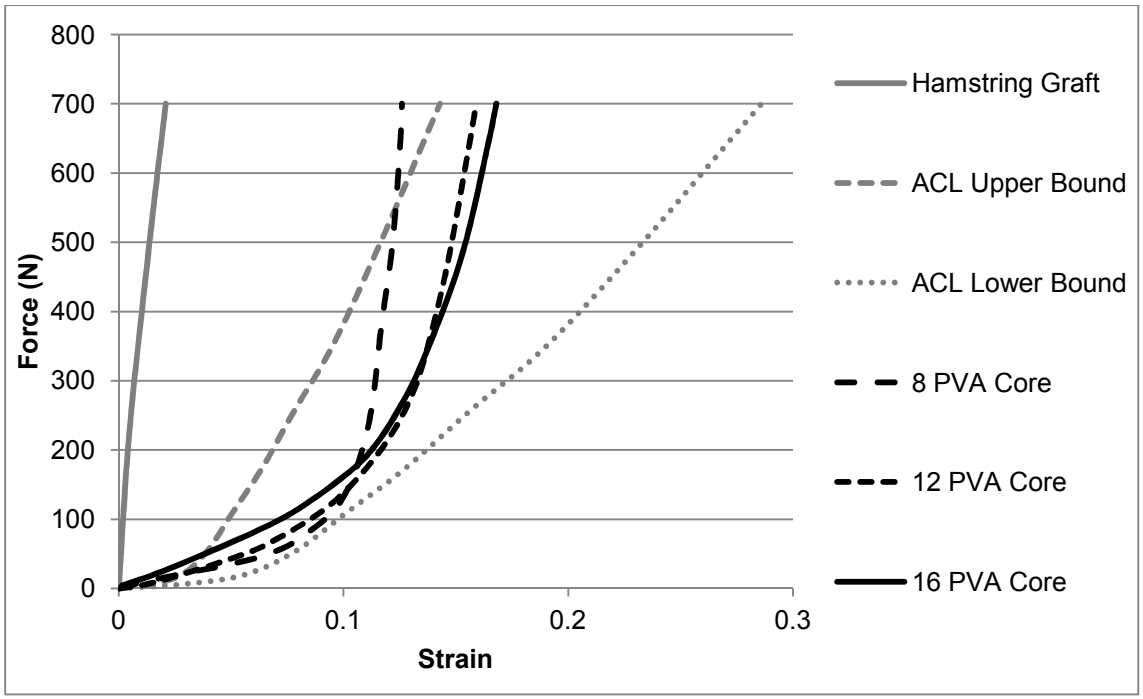

Figure 3.10 Force versus strain relationships for hollow braided samples with 8, 12, and 16 PVA cords in the core shown with the native ACL and hamstring autograft.[2, 13, 19]

Next, the effect of helix angle was studied by comparing hollow braided samples with 16 PVA cords in the core and 12 UHMWPE threads braided around the outside at helix angles of 40°, 45°, 50°, and 55°. Experimental tensile test results were compared to the computed analytical results and the response of the native ACL. The circumferential braid dimension, X_0, was determined by the size of the core and measured to be 2.1 mm in all tested samples. Increasing the helix angle had the effects of increasing the span of the toe region and reducing the stiffness at higher levels of load and strain. Experimental results in showed good agreement with the analytical solutions. Study 3 demonstrated that the best match to the native ACL behavior was

provided by samples with 12 UHMWPE threads braided around a core of 16 PVA cords with a braid helix angle between 40° and 50°.

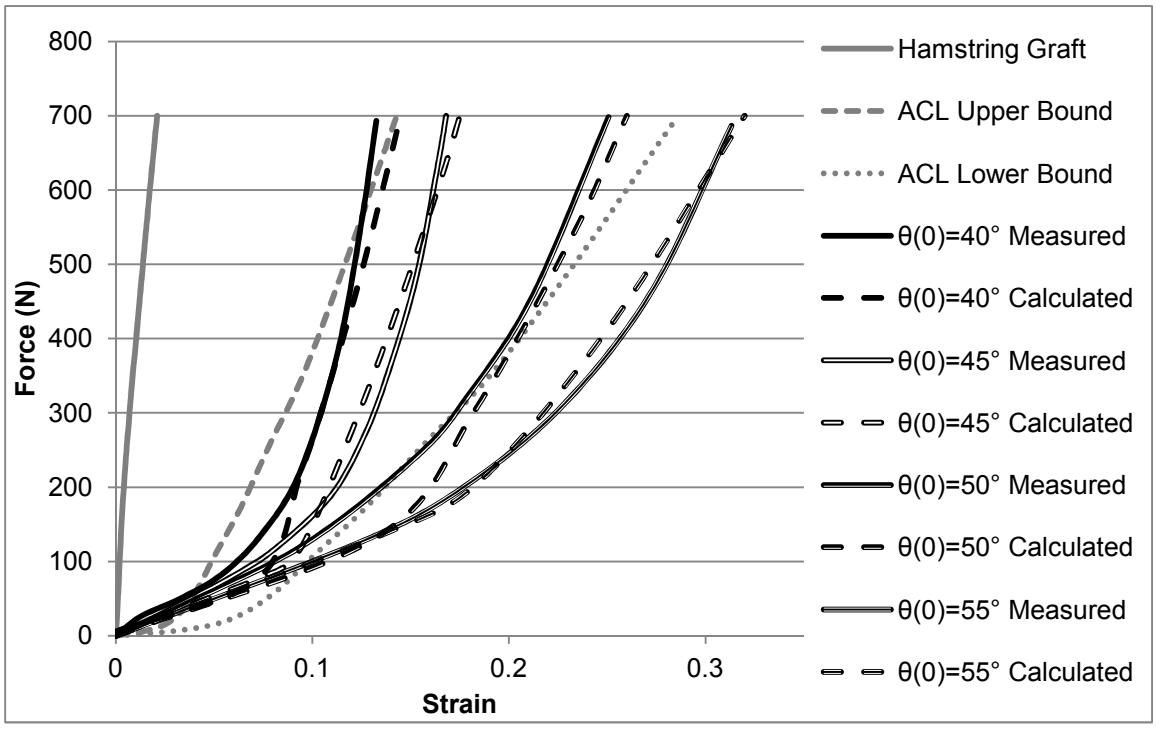

Figure 3.11 Predicted and experimentally measured force versus strain relationship for hollow braids with 16 PVA cords in the core and helix angles of 40°, 45°, 50°, and 55° shown with the native ACL and hamstring autograft.[2, 13, 19]

Table 3.2 Mechanics design inputs with verification test results

Design Input	Target Value	Value attained with 16 PVA cord + 12 UHMWPE thread hollow braid
Stiffness	35-400 N/%	63-179 N/%
Ultimate Load	> 1730 N	> 4000 N
Toe-Linear Region Transition Strain	2-15%	6-15%
Ultimate Strain	> 12%	> 31.6%
Diameter	< 10 mm	8 mm

3.3.4 Study 4: Long-term evaluation

Hollow braided samples were able to withstand cyclical loading over the physiological force range up to 1 million cycles, the point at which testing was stopped. The stiffness remained within the acceptable range and slightly increased over the

course of loading, due to slight bedding in of the UHMWPE fibers into the PVA core. Slippage at the clamps made an accurate determination of permanent elongation difficult; however, the test revealed that the upper bound for permanent elongation after 1 million cycles was about 10%. Gradual progression of minor fraying and wear of the outer PVA core fibers was also observed, likely a result of abrasion from contact with the UHMWPE threads. This damage was not detrimental to the mechanical function of the samples. A separate test on a braided construct with the equivalent quantity of UHMWPE and 22 PVA cords was able to withstand more than 4.5 million cycles before rupture. The results of Study 4 demonstrated that the long-term performance of PVA and UHMWPE composite ropes with the proposed hollow braided structure satisfy the design inputs for resistance to tensile fatigue and permanent elongation.

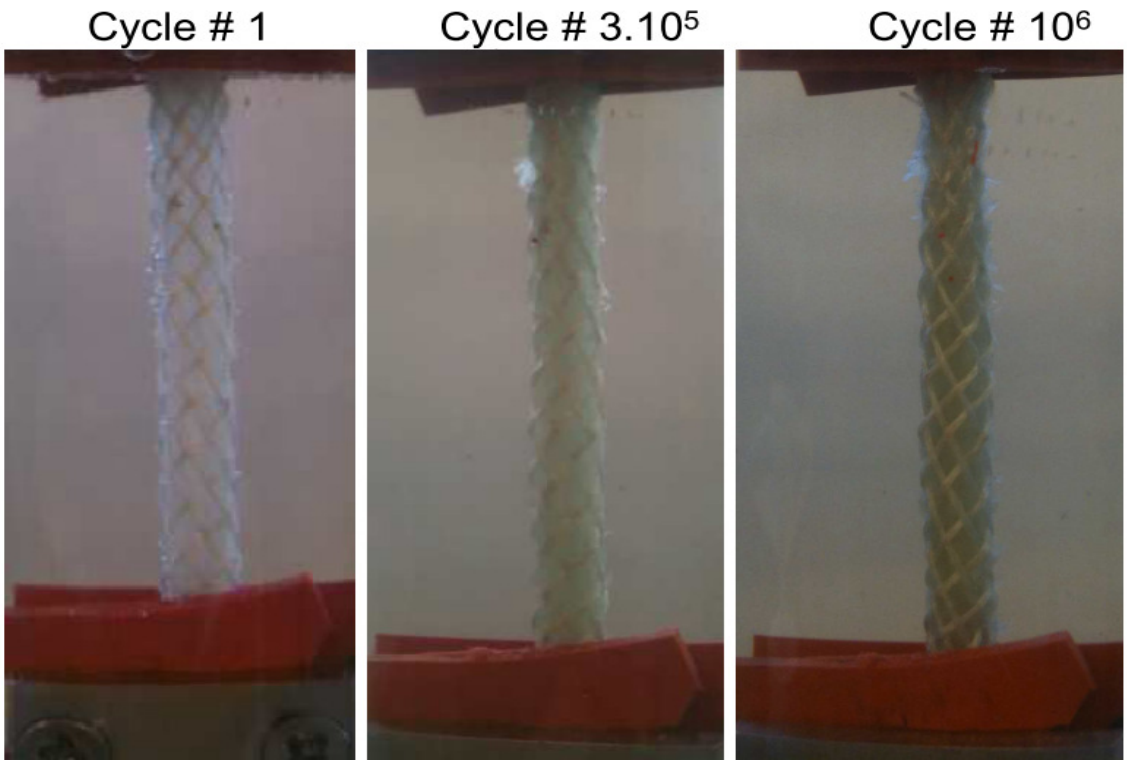

Figure 3.12 Samples at the first cycle, after 300,000 cycles, and after 1 million cycles of loading. Note the minor progression of PVA fraying over the course of cyclic loading.

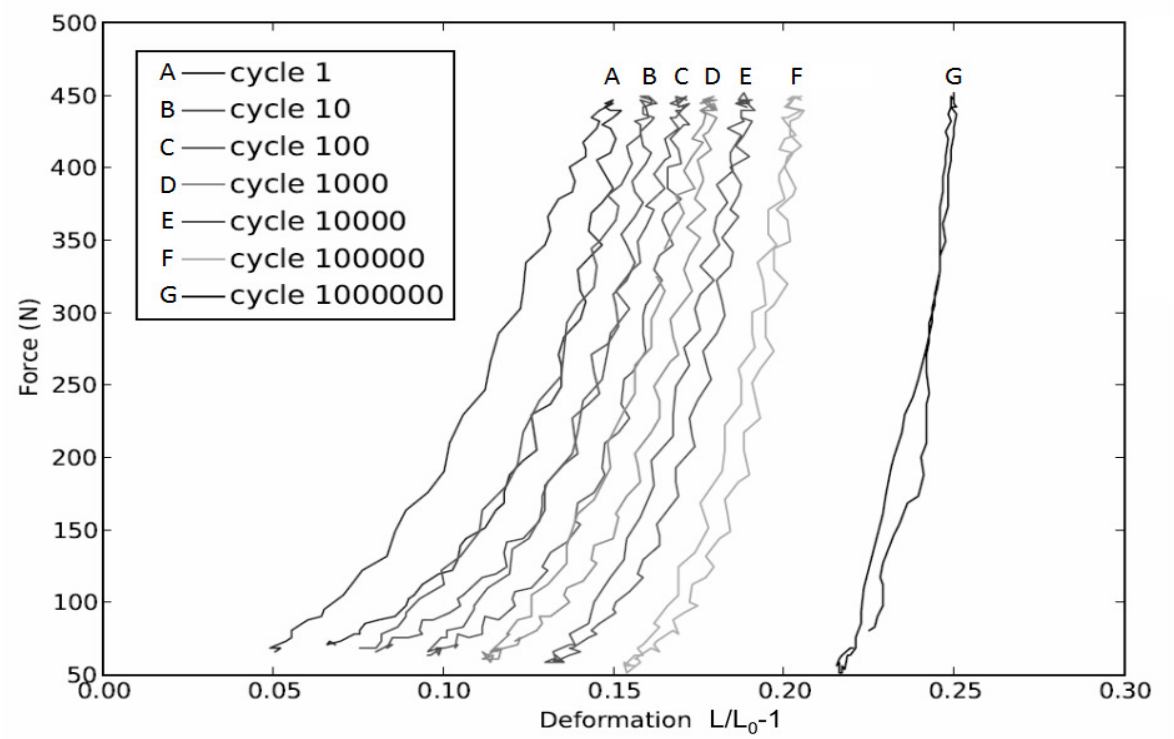

Figure 3.13 Load versus deformation curves over the course of cyclic loading.

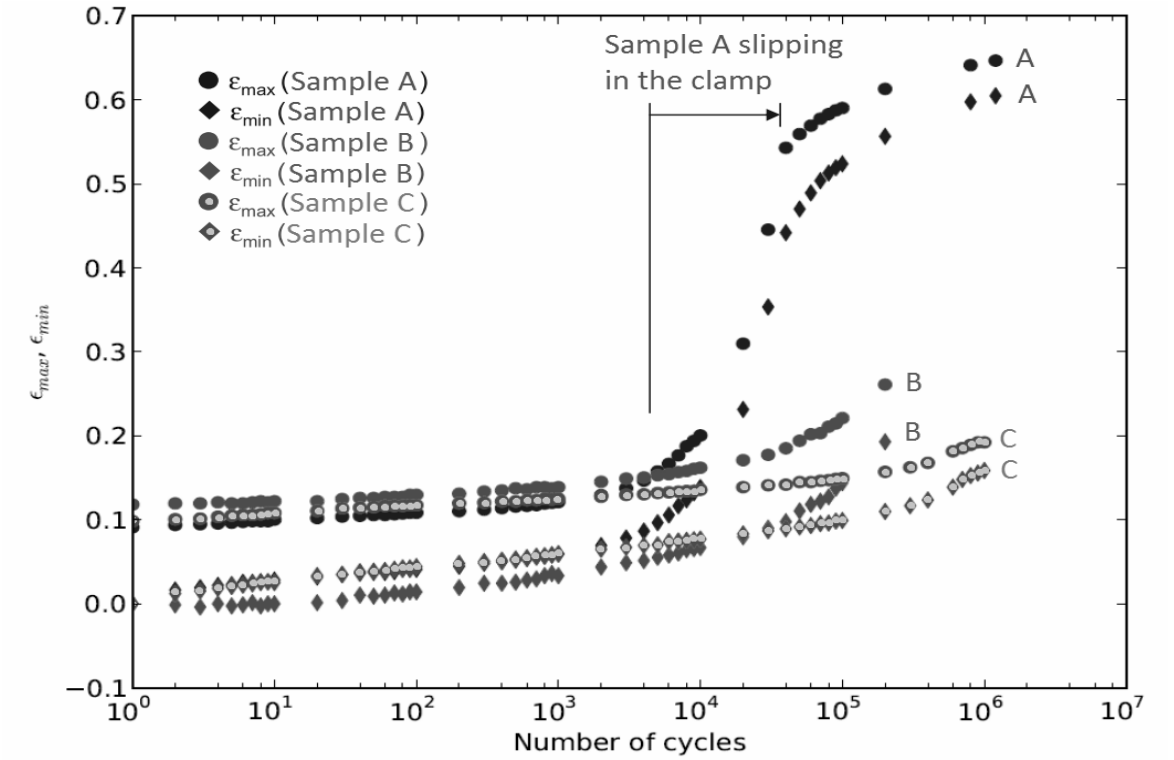

Figure 3.14 Deformation from the application of 50 N and 450 N over the course of cyclic loading. Deformations are calculated relative to the length at the first cycle with the application of 50 N.

3.4 Discussion

Composite structures of PVA and UHMWPE possess adequate mechanical properties to be employed as the ligament-replacing aspect of a prosthetic ACL device with the desired mechanical response provided by a hollow diamond braid with UHMWPE threads around a core of PVA cords in parallel. This arrangement was capable of producing a response between that of only PVA or UHMWPE over the functional force and strain ranges, demonstrating clear superiority over twisted or 4-strand square braided structures, which had distinguishable strain ranges where the response was either strongly dominated by PVA or UHMWPE. The quantity of twelve UHMWPE threads was selected to provide an ultimate load double that of the native ACL, providing a 100% safety factor to reduce risk of rupture. It was found that increasing the amount of PVA in the core reduced the contribution of UHMWPE at higher levels of strain resulting in stiffness closer to the native ACL. The quantity of sixteen PVA cords was selected for the core as it was the maximum amount that could be included before increasing the diameter of the device beyond that of an average hamstring graft. The final parameter to be defined was the helix angle of UHMWPE threads in the braid, found to closely reproduce the tensile response of the native ACL when laid at an angle of 40° to 50° to the ligament axis. Utilizing the described structure, verification testing demonstrated that the design inputs for the toe region effect, ultimate strain, and resistance to fatigue and permanent elongation were satisfied.

A prosthetic ACL with the mechanical behavior and performance provided by the proposed design would have advantages over the currently available ACL replacement options and earlier prosthetic devices. Disadvantages associated with current options that would be eliminated with a functional prosthetic alternative include donor site morbidity and the need for the harvest operation in the case of autografts and disease

transmission risk, slower incorporation, and additional procurement expenses in the case of allografts.[5-6, 32-33] Many of the earlier prosthetic ligaments such as the polytetrafluoroethlyene (Gore-tex), polyethylene terephthalate (Dacron), polypropylene (Kennedy LAD), and carbon-fiber (ABC) grafts had poor biocompatibility resulting in chronic synovitis and effusions.[6, 34-35] PVA and UHMWPE were selected for the proposed design based upon a demonstrated history of good biocompatibility in other biomedical implant applications.[20-23] The ultimate strength of the proposed design was measured in excess of 4000 N which is greater than scaffolds used for tissue engineered ligaments and other previous permanent prosthetic devices such as the Leeds-Keio, Dacron, and ABC prosthetic ligaments which were observed to be susceptible to rupture as a failure mode.[6, 36-38] Though the proposed design is slightly inferior in strength compared to the Gore-tex graft, rupture was not observed among the most prominent failure modes for that device.[6, 36] Another potential advantage of the proposed design is the inclusion of the toe region, which was not noted in the literature as a feature engineered into any of the previous devices. Several authors have suggested that the inclusion of a low stiffness toe region may be important for prevention of creep and fatigue.[39-40]

The mechanical evaluation had several limitations. The determination of visco-elastic elongation from long term loading may or may not be due to creep of the polymeric materials. Prediction of permanent elongation is particularly important value to quantify for a ligament replacement since it has been noted as one of the failure modes of previous devices, directly contributing to increases in anterior laxity and knee instability.[6, 16] This critical issue is difficult to model *in vitro* and remains a limitation in the mechanical proof of any ligament. The clamping system for the long-term test was too small to hold samples of the full size of the proposed design. Therefore, samples

containing only half the quantity of PVA were tested. The full ligament may distribute loads differently such that fatigue life may change. Slippage during the long-term test prevented the determination of a definitive value for the progression of permanent elongation and instead made the measured value from the clamp displacement an upper bound for the possible permanent elongation that may have occurred. Video or photographic tracking of the displacement between marks along the sample length could be used to directly measure sample elongation over the course of cyclic loading distinguishing it from the clamp slippage contributing to the change in clamp displacement. Alternatively, simpler monotonic tension tests might be less susceptible to slippage and still provide a meaningful measurement to predict permanent elongation.

Most of the fatigue tests were ended prior to rupture, leaving the total number of cycles to failure yet to be determined. Loading was limited to 450 N as this was the highest value for normal activities; however, loads as high as 700 N occur *in vivo*.[9, 29] A future test may involve loading at higher and lower magnitudes continuing until rupture so that a complete S-n curve can be generated.

Bending creep and fatigue are other factors that were not fully characterized in this thesis. While important conceptually, these tests are not standard and may or may not have relevance to *in vivo* ligament performance. The cyclic loading test was performed in force control mode as opposed to displacement control mode, though the native ligament or a ligament replacement would also be subject to some degree of displacement constraints. Testing in force control mode provided a more strenuous evaluation, giving an upper bound value on the possible permanent elongation and fatigue *in vivo*. As the ligament undergoes creep beyond a certain point, the other ligaments, muscles, and surrounding tissues would provide restraint to anterior translation, placing a limit on the total amount of displacement, and consequently, the

total amount of elongation. The contributions to tibial restraint provided by the surrounding tissues as the ACL extends or reduces in stiffness has not been studied extensively and biomechanically quantified; therefore, the degree to which the measured results differ from what would be observed *in vivo* remains unclear. Progression of device elongation to the degree resulting in restraint to anterior tibial translation being only provided by the surrounding tissues is precluded by the specified design input, which is exceeded before that extent of elongation occurs.[11]

Efforts were made to simulate the *in vivo* environment by performing the static test on wet samples immediately after 24 hours of submersion in water and by performing the long term test with the samples submerged in water both at room temperature. To better simulate the *in vivo* condition, a physiological fluid at 37°C might be used in future tests. The tests carried out in this study were all one-dimensional tension tests, however other mechanisms contributing to device failure including bending and abrasion were not evaluated.

Another more general limitation is the unsolved problem of developing an *in vitro* test with predictive value for the long-term *in vivo* condition, a weakness criticized previously in the literature.[41] For example, the Gore-tex ligament was tested to failure at $4x10^9$ cycles and with creep of 4% up to $3x10^8$ cycles up to 285 N, predicted to be equivalent to 950 years and 70 years of *in vivo* use, respectively.[42] Despite this high level of performance *in vitro*, both elongation and rupture were observed in as little as 4 to 5 years *in vivo*.[41-42] This deviation between the results predicted from *in vitro* testing and the observed clinical behavior bring to light the importance of long-term *in vivo* studies in the next stage of device development and evaluation.

3.5 Conclusion

PVA and UHMWPE, both noted for good biocompatibility, were utilized in a hollow braided rope structure designed to produce a tensile behavior similar to that of the native ACL. Additionally, the design was tested with applied cyclic loading to 1 million cycles and found to have good resistance to fatigue and permanent elongation. The promising results of mechanical testing of the ACL prosthesis justify more extensive *in vivo* evaluation. A prosthetic alternative to biological grafts would provide advantages for patients and surgeons and would be a significant advance in the field of ACL reconstruction.

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CHAPTER 4 Augmentation of Bone Tunnel Healing in Anterior Cruciate Ligament Grafts: Application of Calcium Phosphates and Other Materials

4.1 Introduction

In all types of anterior cruciate ligament (ACL) reconstruction, a proportion of grafts fail due to a lack of healing in the bone tunnel or abrasion of the graft at the tunnel exit.[1] It has been suggested that stable bone tunnel healing is desirable for an ACL graft to be successful [2] and that the acceleration of the healing between a soft tissue (tendon) graft and bone may allow earlier return to functional activities and improve clinical outcomes.[3] Unsatisfactory osseointegration of tendon grafts used for the replacement of ACL may also be associated with postoperative anterior-posterior laxity.[4] It may therefore be expected that improvements in bone tunnel healing, including ingrowth or ongrowth of tissue around the graft, will improve fixation strength and limit graft failures by pullout and loosening.

A variety of materials have been applied in the bone tunnels in order to improve healing. These range from autologous bone tissue or cells to proteins and calcium salts. In particular, a number of studies have proposed the use of calcium phosphate (CaP) materials for this purpose. The application of CaP to soft tissue attachments is becoming more common and has been shown to induce increases in fixation strengths and bone formation.

This review examines the hypothesis that the application of CaP can improve bone tunnel fixation and healing in ACL grafts. The evidence for the usefulness of CaPs in ACL replacement is discussed along with evidence for the efficacy of CaP in other relevant applications and other materials used for bone tunnel healing improvement. The

following section gives a brief introduction to ACL replacement, mechanisms of bone tunnel healing, and methods commonly used to assess healing.

4.2 Bone Tunnel Healing in ACL Replacement

4.2.1 ACL Anatomy and Injury

The ACL is one of two ligaments located in the centre of the knee joint. It has insertions in the tibia and distal femur and has a microstructure made up of collagen bundles surrounded by a complex matrix.[5] The ACL restricts anterior tibial translation and gives stability in rotation. Failure to treat this type of injury may lead to mechanical instability in the knee and has been linked to the early onset of osteoarthrosis.[6] Damage to the ACL may occur from both contact and noncontact mechanisms of injury.[7] It is common both in the general population and, more particularly, in those taking part in sporting activities. A recent study based in the United Kingdom identified the rate of ACL injury at 8.1 instances per 100,000 people per year.[8] Reconstructive surgery is routinely carried out for patients with a torn or ruptured ACL. In the USA, around 200,000 ACL reconstructions are performed each year.[9] The reader is referred to recent reviews for detailed information on ACL anatomy, function, and injury.[5, 10-11]

4.2.2 ACL Replacement

The ACL does not heal when torn because it lacks sufficient vascularisation. Surgical reconstruction is the standard treatment in sports medicine for ACL rupture.[5] Patients with ACL injuries are typically younger and more active than other orthopaedic patients, and reconstructions should exhibit good longevity, withstanding high stresses over millions of cycles.[12] However, the outcomes of the various techniques used for ACL replacement have not always been positive. Patient selection and implantation technique have contributed to poor results from artificial grafts, allografts, and autografts.

Over the past 10 years, technique has vastly improved, making autograft ACL replacement both common and more successful. The procedure is usually carried out arthroscopically using a graft from the semitendinosus tendon or the central third of the patellar tendon. In the latter case, the graft is harvested with a section of bone at each end and interference screws are used to fix the bone plug into place. These are known as bone-tendon-bone (BTB) grafts. A recent review suggests that there is no significant difference in clinical results between autograft types, with factors other than graft donor site (including fixation, damage to the meniscus and articular cartilage, and the requirement of additional surgical procedures) being the most important determinants for successful outcomes.[13]

Once the graft has been harvested and prepared, often by pretensioning and the addition of sutures, tunnels are drilled through the tibia and femur passing through the attachments of the original ligament (see Figure 4.1). The graft is pulled into position and fixed using staples, screws, sutures, or commercially available fixation devices such as the cross-pins or interference screws. The surgical fixation is the weak point of the graft in the early postoperative stages and remains so until bone tunnel healing occurs.[14]

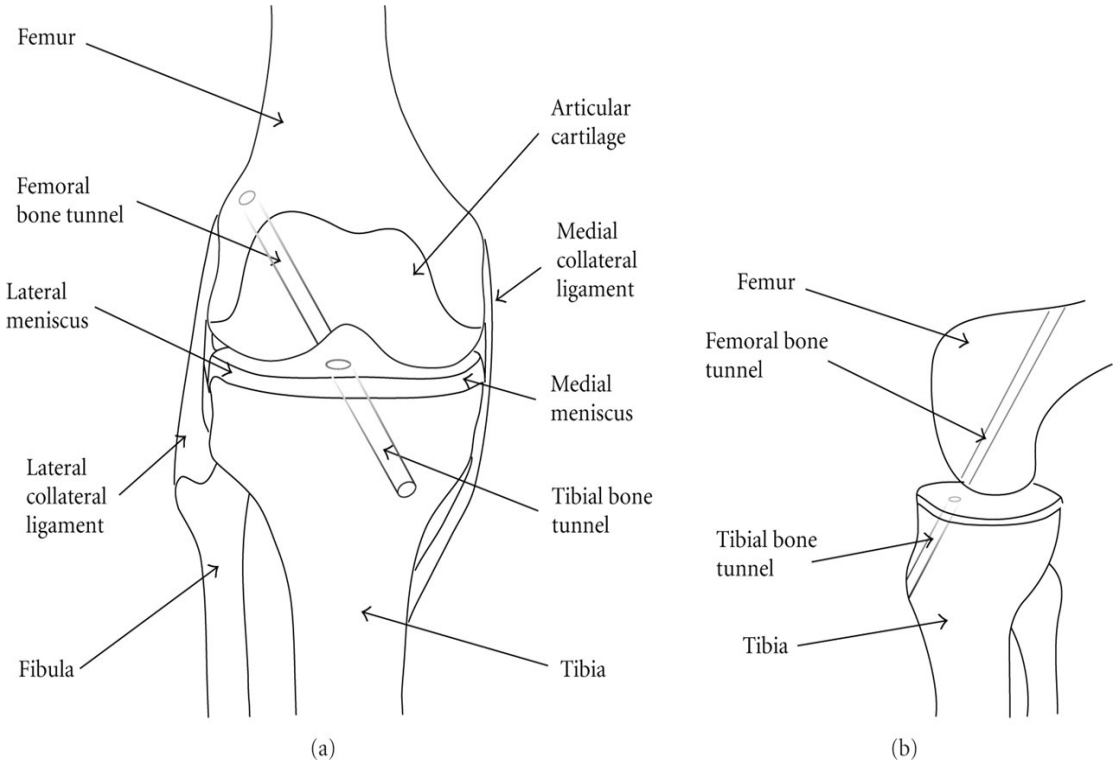

Figure 4.1 The anatomy of the bones of the knee showing the position of the bone tunnels from (a) frontal and (b) lateral views. The patella and patellar tendons are omitted for clarity.

Autografts for ACL replacement have limitations including limited availability, and adverse functional changes including muscle weakness at the donor site. Conversely, artificial or tissue-engineered ligament grafts have some distinct advantages. These include the ability to control manufacturing, condition, quality, sterility and size of device before implantation. Mechanically tested and controlled grafts could be made available off the shelf and eliminate the need to create a second defect site through the harvesting of healthy tissue. Unfortunately, the majority of artificial ACLs have suffered from high failure rates due to mechanical, and in some cases biological, influences and have been removed from the market.[12] In the early postoperative stages, the majority of these failures occurred in the bone tunnels.

4.2.3 Bone Tunnel Healing

The insertion of the native ACL is characterised in four layers: tendon, fibrocartilage, mineralised fibrocartilage, and bone. The collagen fibres of the tendon extend into both the fibrocartilage, and the mineralised layer. This structure is usually destroyed when the ligament is removed and the bone tunnel is drilled. A replication of this direct type of insertion may be considered desirable when assessing bone tunnel healing for ACL grafts.

The mechanism by which graft-bone healing occurs depends on the type of graft used. For BTB grafts, healing in the tunnel resembles normal fracture healing, but may be a more complex process. Incorporation of the bone block in the tunnel has been observed as early as 16 weeks after surgery.[15] BTB grafts have the advantage of allowing rigid fixation of the graft in the bone tunnel.

The tendon-bone healing process occurs through a different mechanism after implantation of a soft tissue graft without bone plugs.[15] Firstly, fibrovascular tissue forms between the graft and bone and becomes mineralised. The tendon tissue itself is then mineralised and incorporated into the bone.[16] Sharpey's fibres are made up of type I collagen and connect the periosteum to the bone. The formation of Sharpey-like fibres within the bone tunnel is often identified as a marker of indirect healing between the tendon and bone.[17] The formation of these collagenous fibres may occur from six weeks after surgery. However, complete bone tunnel healing of an ACL graft may occur as late as six to twelve months after surgery.[15] Some studies in animals have suggested that tendon graft incorporation occurs more slowly than BTB healing.[2]

In addition to the choice of graft, surgical fixation, and graft position, interfacial motion within the bone tunnel may affect healing.[2] Graft motion within the bone tunnel has been shown to be inversely proportional to healing in an animal model.[18]

4.2.4 Assessment Techniques for Bone Tunnel Healing

Three main factors are commonly assessed to evaluate bone tunnel healing after ACL replacement: functional outcome, biological structures, and mechanical properties. In clinical studies, functional outcome is measured by patient satisfaction, pain levels, and scores in the International Knee Documentation Committee (IKDC) and Knee injury and Osteoarthritis Outcome Score (KOOS) tests. In both clinical and animal studies, the biological structures in the bone tunnel are examined using noninvasive imaging. In animal models, these structures can also be examined by the excision and histological examination of the graft-bone construct. This method can be used to identify collagen fibres, calcified tissue and different types of cell found in the bone tunnel. Imaging techniques include the use of X-rays for the assessment of bone tunnel width and, more recently, the use of CT scanning to quantify the amount of bone tissue formed within the tunnels.

Biomechanical tests are carried out on the tibia-graft-femur construct following *in vivo* studies in animals. This testing yields strength and stiffness data, as well as permitting observation of the mode of failure of the graft. The explanted bone-graft construct is mounted in a tensile test machine and, most commonly, extended to failure at a constant rate. The ultimate tensile strength (UTS) is recorded, and graft stiffness may be calculated. Direct comparison of data from these tests is complicated by differences in angles of flexion chosen when mounting the bones for the test as well as variations in extension rate, pretensioning or cyclical loading of the graft and the type of animal model used. In particular, the rate of extension may influence the mechanical behaviour of the graft.[19]

Two distinct modes of failure are reported in tensile testing. Pullout is the term commonly used to indicate a failure of the fixation or tendon-bone interface. The pullout

strength of a graft is the force required for failure to occur by this mode. The UTS of a graft may refer to pullout or to midsubstance failure, which describes the rupture of the graft material itself or, in some cases, the deformation of the graft beyond a functional length. The majority of studies combine load-to-failure data, irrespective of the mode of failure which occurred. It is expected that failures in the early postoperative stages will occur in the bone tunnel, with midsubstance failure becoming the more common mode as bone tunnel healing advances, leaving the soft tissue graft itself as the weakest point in the construct.[14] A difference in the mode of failure occurring in experimental and control groups may therefore be interpreted as an indication of an increase in strength of the bone-graft interface, assuming the bone healing enhancement does not weaken the graft.

4.3 Calcium Phosphates

4.3.1 Calcium Phosphates as Biomaterials

CaPs are considered to be safe, biocompatible materials for use in long-term implantation. They have been used in a variety of applications including hip stem coatings and bone graft materials and are commercially available in injectable, powder, granular, and block forms.

CaP is bioactive: the presence of Ca and P ions allows the formation of a direct chemical bond between the bone and the implant.[20] The exact properties of CaPs depend on the Ca : P ratio, the crystallinity of the material, the presence of water and the purity of the material.[21] Hydroxyapatite (HA) has Ca : P ratio of 1.67 and may be considered as stoichiometric CaP. CaP occurs naturally in the body as the mineral component of bone and enamel in a form resembling HA [28]. β-tricalcium phosphate (β-TCP) is a more quickly resorbed form of CaP. HA is resorbed over a period of decades, while β-TCP resorbs in months.[22] The adsorption of particles on the surface of CaP is

related to its crystallinity and influences the biological response to the material. CaP powders of different sizes have been shown to produce differing rates of bone formation *in vivo* [30]. The reader is referred to a review of bioceramics for more information on general uses and properties of CaP.[23]

In this review, CaP is employed as a general term for calcium phosphate-based materials and is used where the specific type of CaP is not identified in the original study. The specific type of CaP produced or used in a study is identified when possible.

The following section is a review of studies using CaP to improve bone tunnel healing. Both qualitative and quantitative assessments are considered, along with analysis of biomechanical changes induced by the treatments. A summary of the outcomes of mechanical testing from these studies is given in Table 4.1.

Table 4.1 Mechanical testing of different augmentation methods using calcium phosphates for bone tunnel healing. For ease of comparison and where available, data from mechanical testing at six weeks after surgery are given. Results at earlier and later time points are detailed in the text. Where six week data is not available, the nearest time period is included. [a]These values were calculated from the average values in the preceding two columns. [b]Reflects a difference in the predominant mode of failure from pullout failure in the controls to midsubstance failure in the treated subjects. [c]This is a low-porosity CaP control, not a nontreated sample.

Augmentation method	Average increase in strength (as% of control)[a]	Ultimate tensile strength in treated group (N)	Ultimate tensile strength in control group (N)	Change in mode of failure[b]	Time (wks)	Ref.
Brushite calcium phosphate cement(CPC)	118%	94±42	43±11	√	6	[24]
Injectable tricalcium phosphate cement(TCP)	87%	62.90±7.62	33.60±5.78	√	4	[25]
Injectable CaP cement	110%	11.491±2.865	5.253±3.995	x	2	[26]
Injectable CaP with magnesium	65%	71.8±31.8	43.4±14.8	x	6	[27]
Hybridization by CaP precipitation	Not statistically significant	116.9±48.3	109.4±47.2	2/7 failed by pullout in treated group, 3/7 in control	6	[28]
Bulk CaP with interconnected pores	116%	12.8±5.9	5.0±1.8[c]	x	6	[29]

4.3.2 Calcium Phosphates in ACL Reconstruction

4.3.2.1 Injectable Materials

A short-term biomechanical study on the effects of CaP cement on the pullout strengths of tendon grafts for ACL replacement was carried out using a rabbit model by Tien et al.[26] Grafts were implanted bilaterally and held in place with sutures. One graft in each subject was then further fixed in place by injection of the bone cement into the tunnel. The application of the cement led to increase in pullout strength, with the average

strength more than doubled as measured two weeks after surgery. Biomechanical testing was not carried out at later time points. Histological examination showed bone islands growing between the cement, bone and tendon as early as three weeks after implantation. Bone development extended to 24 weeks after surgery. In the noncemented control subjects, no bone formation was found in the interfacial gap.

These findings are supported by Huangfu and Zhao, who examined the use of injectable resorbable TCP in bone tunnels in a canine model.[25] The grafts filled only the articular ends of the tunnels and were fixed using sutures. The CaP was then used to fill the sections of the tunnels not filled with the graft. Although the TCP was not specifically injected into the tendon-bone interface, it was observed to be present in that area during histological evaluations. At 12 weeks after implantation, in the experimental grafts, areas resembling a normal ACL insertion appearance with fibrocartilage and calcified bone were present. The remainder of the interface showed a regular Sharpey-like fibre link from tendon to bone. Bone development in the controls was found to be slower, with no calcified tissue or fibrocartilage formed. The pullout strength of the grafts was found to be increased by the presence of the TCP up to six weeks after surgery. While earlier results were statistically significant, the significance of data gathered at the six week time point was limited by the size of the sample. From eight weeks after surgery, all failures in the test group occurred by mid-substance rupture. This study established a clear pattern of improved intratunnel healing up to 12-weeks after surgery.

The authors of these studies do not discuss whether the observed improvement in healing was the result of the restriction of graft movement in the tunnel due to the presence of the cement or of increased bioactivity due to the chemical effect of the CaP. Huangfu and Zhao do, however, speculate that the use of a resorbable material is preferable if a normal ligament-bone insertion is to be developed.[25]

In a further study examining the effects of CaP-based cements, a cement containing brushite (dicalcium phosphate dihydrate) was shown to increase fixation strengths in ACL grafts up to 12 weeks after implantation in a rabbit model.[30] The increase in strength was 118% six weeks after surgery and 55% at the 12 week time point. The cement was injected into the bone tunnels before the grafts were pulled into place. *In vivo*, the cement degraded to leave granules of β tricalcium phosphate between the bone and tendon. The majority of failures in the treated group occurred in the intra-articular section of the graft, whereas control grafts failed by pullout. The increase in strength corresponded with larger amounts of bone formation around the tendon graft.

Gulotta et al. investigated the use of an alternative to standard injectable CaP materials by adding magnesium to the cement.[27, 31] While standard CaP cements act as grout, filling the space between the bone cavity and the graft, the inclusion of magnesium was intended to give this product adhesive properties. The study was carried out in a rabbit model, and grafts were held in place using sutures. In the control group, no cement or adhesive was applied. Three weeks after surgery, the strength of the experimental group was the same as that of the controls. However, this may have resulted from incomplete hardening of the adhesive at this stage. Six weeks after surgery failure loads were 65% higher than the controls. The failure of the grafts is described as occurring at the “graft-tunnel junction.” The authors note that although the graft fixation strength was increased in this study, it did not achieve the strength of an unoperated tendon. The average ultimate load-to-failure of the native rabbit ACL has been shown in a previous study to be 351.8 ± 41.6 N (Labs 2002 cited by [27]), while mean load to failure in the treated group was 71.7 N.[27] This study also made use of μCT scanning to quantitatively measure the increase in bone volume in the tunnels. A significant increase in total intratunnel bone volume was observed in the experimental

group when compared to control at six weeks. Staining also showed more cartilage tissue and less fibrous tissue formation in the bone tunnels. The increase in cartilage formation was shown to be statistically significant at six weeks after surgery, as evidenced by an increased area of metachromasia (79 556.2 ± 61 664.0 μm^2 compared with 2806.2 ± 6 873.7 μm^2 for the control).[27]

Although the results of this study show improvement when compared to controls in which no bone adhesive was used, the role of the magnesium in this improvement has not been proven. When comparing the results of this study to others using CaP cements, there does not appear to be an increase in strength corresponding to the presence of the magnesium (see Table 4.1).

It is important to note that the use of bone cements in ACL graft attachment without additional surgical fixation has been shown to result in inadequate fixation.[32] An *in vitro* study in porcine bone compared various methods of surgical fixation, including a calcium carbonate-containing cement. High levels of graft slippage within the bone tunnels were observed during cyclical loading, showing the bone cement to be unsuitable as a primary fixation method.

A different injectable material was proposed by Ishikawa et al.[33] Collagen gels containing HA for the improvement of tendon-bone healing were tested in a rabbit model. A direct bond was shown to be formed between the tendon and the bone in the presence of the gel, which contained 60% HA and 40% collagen. The HA particles were up to 200 μm in size. The presence of both the collagen and the HA resulted in collagen fibres from the tendon being interwoven into newly formed bone around the graft. In the controls, in which no gel was applied, amorphous tissue formed in the tendon-bone interface. The effect of the improved interface on the mechanical performance of the graft was not assessed.

4.3.2.2 Bone Screws in ACL Reconstruction

A further means of introducing CaP into the bone tunnel is to include them in the material to be used in the fixation of the graft. This commonly involves the use of resorbable fixation screws containing CaP. A number of studies have examined the use of CaP-containing interference screws for soft tissue graft fixation. Hunt et al. compared bone tunnel healing for grafts fixed with commercially available PLLA-HA composite screws with that for grafts fixed with simple PLLA screws in ovine models over a period of 12 months.[34] New bone formation along the perimeter of the screw threads was found to be significantly increased in screws containing HA than those containing PLLA alone. These observed increases in bone ingrowth and mineralisation can be directly attributed to the presence of the HA as the mechanical fixation of the two types of screw is comparable. The mechanical properties of the fixations and the phenomenon of bone tunnel widening were not investigated.

The same composite screws (HA/PLLA) have also been examined *in vivo* in a clinical setting in 100 patients.[35] The results supported those of Hunt et al., with a reduction in tibial tunnel widening occurring around the screw in cases where the composite screws were used. It is interesting to note, however, that above the screw, in the section of the tunnel containing tendon graft, bone tunnel widening was unaffected by the type of screw used. This suggests that the effect of the HA is highly localised. The improvement in bone tunnel healing around the screw did not correspond to any difference in clinical outcome or knee laxity. However, this study was carried out 12 months after surgery. More differences between the experimental and control groups may become apparent at later time points.

4.3.2.3 Precipitation of CaP

In contrast with other methods which seek to apply CaP in the bone tunnel or include it in the fixation, Mutsuzaki et al. deposited a layer of CaP directly onto a tendon graft.[28, 36] This was achieved by soaking the ends of the tendon in Ca-containing solution and a PO4-containing solution in turns for 30 seconds each. The complete soaking process took ten minutes, and the CaP layer deposited was over 100 μm thick. XRD analysis showed the deposited material to be made up of low-crystallinity apatite and dicalcium phosphate dihydrate. The deposited CaP was examined by transmission electron microscopy and was shown to be made up of needle-like crystals formed on and between the collagen fibrils of the tendon.[28]

When implanted in white rabbits, the “hybridized” tendons appeared to heal faster than controls which had been soaked only in saline. As early as 5 days after surgery, increased numbers of osteoclasts and osteoblasts were observed in the experimental tendons compared to the controls. Over a period of four weeks, tendon-bone healing was more advanced in the healing group, particularly in the formation of a direct tendon-bone bond, without the layer of interfacial fibrous tissue observed in the controls.[36] Although the later study implanting hybridized tendons in goats failed to find a corresponding increase in UTS six weeks after surgery, a slight change in the failure mode was observed between experimental grafts and controls.[28] Failures in the CaP treated grafts occurred in the intra-articular portion, whereas three of the seven control grafts failed by pullout from the bone tunnel. The authors claim that this implies that the fixation in the CaP grafts is stronger than that in the controls and may be related to the earlier observation of improved bone tunnel healing; however, the assessment is not statistically significant. The studies were carried out six weeks after implantation.

In addition to studies directly investigating bone tunnel healing, CaPs have been used for enhancement of the attachment of other soft tissues grafts to bone. The following section presents the outcomes of investigations into these applications of CaP-based materials.

4.3.2.4 Calcium Phosphates in Other Relevant Applications

The use of porous CaP blocks has been suggested as a means of attaching tendon to bone. Although their study was not based on an ACL replacement procedure, Omae et al. examined healing between two types of porous CaP and tendon grafts implanted with them in rabbit femora.[29] The two materials tested were both commercially available in Japan. The first had a pore size around 150 μm, was 72%–78% porous and was made up predominantly of interconnected pores. The second material had a pore size of 50–300 μm and 35%–48% porosity with a lower level of pore interconnection. Wedges or cylinders of the CaP were implanted in the bone with cylindrical holes allowing the tendon graft to be passed through the block. The material with the interconnected porosity induced the best healing, with early formation of collagenous tissue followed by bone ingrowth into the material. Twenty-four weeks after surgery the tendon was found to be in direct contact with the bone grown into the CaP material. The amount of biological ingrowth into the other material was found to be lower. This was a predictable outcome due to the lack of interconnectivity in the porous material. The improved ingrowth in the interconnected material resulted in an increase in tendon pullout strength. This paper does not, however, comment extensively on the healing between the CaP and the tendon, focussing instead on the extent of bone ingrowth into the porous material. An extension to this study found that seeding bone marrow stromal cells into the interconnected CaP ceramics further improved bone

attachment.[37] This procedure could be considered a step towards replicating a BTB graft by artificial means.

CaP is also used as a synthetic bone graft and has been proposed for use in a variety of forms as a scaffold component for tissue engineering. Some of these applications may be transferable to ACL graft fixation, particularly in the development of artificial grafts. The following brief review summarises investigations of CaP which may be relevant or applicable to ACL graft development.

Al Munajjed and O'Brien produced collagen scaffolds and coated them in precipitated hydroxyapatite by serial soaking in calcium chloride and ammonium sodium hydrogen phosphate solutions.[38] The scaffolds produced were not sufficiently strong for implantation in bone without support, having a compressive modulus of 10.3 KPa. However, this material combination may have applications in bone tunnels, particularly if the collagen-CaP structure could be tailored to encourage regrowth of a gradual structure mimicking the natural ACL insertion.

Mavis and Demirtas used a simulated body fluid-like solution to deposit nanoscale HA particles on polycaprolactone nanofibres. The aggregation of the HA did not compromise the porosity of the resulting scaffold. The presence of HA was shown to increase the attachment and proliferation of osteoblast-like (MC3T3) cells on the scaffolds *in vitro*.[39] Other HA-containing polymer composites proposed for bone tissue engineering include HA-Poly(ester urethane), which was shown to retain its viscoelastic properties and biocompatibility after HA incorporation [40] and HA-polyamide.[41]

The development of synthetic materials for the replacement of articular cartilage has advanced in recent years. The production of compliant materials which mimic more closely the properties of natural cartilage necessitates the development of a means of fixing the graft to the underlying bone. As suggested by Sinha and Guha, the

incorporation of HA into an appropriate scaffold material may facilitate fixation to bone tissue.[42] In this study, HA-PVA hydrogels were obtained via the freeze-thawing of a PVA emulsion in which HA particles had been made to precipitate. The resulting scaffolds were porous and the authors suggest that it may be possible to induce a gradient in the HA concentration through the structure, making it suitable for bone-cartilage tissue engineering.[42] Similarly, Wu et al. investigated a PVA hydrogel for cartilage replacement.[43] The HA particles were found to increase elastic modulus of the material. *In vitro*, the presence of HA also increased apatite formation when submerged in simulated body fluid. This is often interpreted as a sign of bioactivity and is a commonly observed phenomenon in HA-containing materials.[44]

These promising *in vitro* indications are complemented by a further study which included an *in vivo* evaluation. An HA-PVA hydrogel construct with a graduated HA content was fabricated by a sol-gel method by Zheng et al. and tested both *in vitro* and *in vivo*.[45] PVA does not usually adhere to cartilage and living bone. After immersion in SBF, only HA-containing materials were coated in a bio-mineralised CaP layer. This corresponded to good bonding and osteoid development between the subchondral bone and the synthetic material when implanted in the femoral heads of rabbits. The authors considered HA-PVA to be a promising articular cartilage construct, particularly with respect to its bone integration.

The addition of HA to PVA in order to improve cell attachment properties was also put forward by Degirmenbasi et al.[46] for use in articular cartilage replacement. The HA/PVA/collagen scaffolds produced were porous, a feature desirable for the encouragement of bone ingrowth. However, the pores produced measured no more than 500 nm, a dimension too small to allow bone ingrowth to occur.[47]

An alternative approach to improving PVA attachment to bone in cartilage repair is to coat the hydrogel attachment surface with a layer of amorphous HA to provide an interface. One study coated the bone-contacting surfaces of a PVA hydrogel construct with amorphous HA using pulsed laser deposition (PLD).[48] This technique has the advantage of allowing targeted deposition which, unlike soaking methods, leaves the articular surface of the PVA clear of HA. When tested *in vitro*, the presence of the 300 nm thick layer of HA greatly increased the attachment and proliferation of murine fibroblasts (L929). The investigation was continued with a study of osteoblast cell (MC3T3) attachment to HA-covered gels.[49] Cell numbers were higher on the HA than on the hydrogels alone, as were both alkaline phosphatase and osteocalcin production. The presence of the HA encouraged osteoblast differentiation. The authors consider this an indication that HA coating by PLD is an effective way of fixing PVA hydrogels to bone.

A recent review considered the range of materials applied for the enhancement of intra-tunnel healing.[2] The following section briefly presents these strategies for the augmentation ACL graft incorporation before comparing their results with those found for CaPs. Table 4.2 summarises the effects on fixation strengths documented for some of the different methods.

Table 4.2 Mechanical testing of various augmentation methods for bone tunnel healing. For ease of comparison and where available, data from mechanical testing at six weeks after surgery are given. Results at earlier and later time points are detailed in the text. Where six week data is not available, the nearest time period is included. [a]These values were calculated from the average values in the preceding two columns. [b]Reflects a difference in the predominant mode of failure from pullout failure in the controls to midsubstance failure in the treated subjects.

Augmentation method	Average increase in strength (as% of control)[a]	Ultimate tensile strength in treated group(N)	Ultimate tensile strength in control group(N)	Change in mode of failure[b]	Time (wks)	Ref.
GCSF	114%	99.45±25.5	31.97±11.9	√	4	[50]
BMP-2 (low dose)	0%	142±50	143±68	√	4	[51]
BMP-2 (high dose)	Not statistically significant	210±66	171±20	√	4	[51]
BMP-7	77%	380±33	215±44	√	6	[52]
Xenograft-derived BMP	52%	64.71±21.36	42.69±15.03	x	6	[53]
Stem cells	122%	55.7 (Range 21-90)	30.6 (Range 18-43)	x	4	[54]
Periosteum	43%	46.9±13.3 N/mm	32.7±13.3 N/mm	√	6	[3]
Periosteum	77%	57.1±16.7	32.23±9.9	2/10 failed by pullout in treated group, 1/10 in control	6	[55]
Periosteum with bone marrow	Not statistically significant	35.39±9.3	32.23±9.9	3/10 failed by pullout in treated group, 1/10 in control	6	[55]

4.4 Alternative Augmentation Materials

4.4.1 Soft Tissue Grafts

4.4.1.1 Biologics

The use of artificial or processed bone proteins and growth factors to augment healing in ACL replacement grafts has been investigated. Granulocyte colony stimulating

factor (GCSF) causes the production of granulocytes and stem cells in bone marrow. It has been shown to induce the differentiation of neutrophils (cells of the immune system associated with inflammation) and to encourage angiogenesis and the differentiation and migration of mesenchymal stem cells. Sasaki et al. therefore proposed that the application of GCSF may encourage accelerated bone tunnel healing. GCSF was incorporated into a gelatin hydrogel to control its release and applied during ACL reconstruction in adult beagle dogs. In biomechanical tests, the treatment resulted in a large increase in the failure load (see Table 4.2). Histological investigations also indicated accelerated bone development around the GCSF treated grafts.[50] The majority of experimental grafts failed midsubstance while untreated grafts failed by pullout, indicating an increase in the bone-graft interface.

Bone morphogenetic proteins (BMPs) are signalling proteins that influence tissue structures in the body. They have been shown to have a role in skeletal development. Both BMP-2 [56] and BMP-7 [52] have been shown to increase graft fixation strengths when applied in the bone tunnels in animal models. Likewise, BMP-7 was shown to increase the volume of bone formed within the tunnels six weeks after implantation.[52] However, one study found that the difference in strength between grafts treated with BMP-2 and controls diminished over time (as measured eight weeks after surgery).[51] This implies that these products induce faster healing, but not necessarily stronger fixations in the long-term.

Chen et al. advanced the study of the use of BMPs by combining them with implanted periosteal progenitor cells.[4] The protein was tested in soluble form (BMP-2 alone) and tethered to the surface to prevent dissipation (BMP-2 tethered with hyaluronic acid). At three and six weeks after surgery, more calcium and collagen were found in the soluble BMP-2-containing samples than in controls, with significantly increased amounts

identified in the hyaluronic-acid tethered samples. At three weeks after surgery, the mode of failure was changed in the hyaluronic-tethered BMP-2 group, in which no samples failed by tibial pullout. Failure strengths were higher in the treated groups than in the control, with the hyaluronic-acid tethered grafts the strongest six weeks after surgery. Similar results to those found for BMPs were observed after application of a bone-derived extract (Bone Protein, Sulzer Orthopaedics).[57] In tensile tests, failure loads were significantly higher than in control groups at two, four and eight weeks after surgery, although the failure modes were unchanged.

Bone samples can be used as a source of natural BMPs. Pan et al. studied the effect of applying recombined bone xenograft within the bone tunnels after ACL replacement.[53] The xenograft was used to produce BMPs, which were then mixed with cancellous bone and formed into cylinders which were attached to the ends of tendon grafts and implanted in the tibial and femoral bone tunnels in rabbit models. The average load to failure of the treated grafts at this time point was 58% greater than that of the controls. Failure strength at 12 weeks after surgery was also increased.

Demineralised bone matrix (DBM) is a further source of BMPs which has been proposed as a means of enhancing tendon-bone healing in rotator cuff repair. Application of this material has been shown to increase fixation strengths between tendon and bone in an ovine patellar model. The presence of the DBM induced an increase in the growth of fibrocartilage and mineralised fibrocartilage at the tendon-bone interface.[58]

These studies demonstrate the importance of the mode of delivery chosen for these proteins, as shown by the differences in results between tethered and nontethered molecules. Longer studies would be beneficial in order to properly evaluate their efficacy. BMPs have been applied in other bone repair applications, producing promising results,

and BMP-containing products have been approved by regulatory bodies. The reader is referred to a recent review for further information.[59]

4.4.1.2 Cells

As well as the use of biologics (which include BMPs and GCSF), the application of materials seeded with mesenchymal stem cells (MSCs), from which osteoblasts are derived, has also been shown to increase failure strengths and improve bone tunnel healing. In one such study, MSCs were applied to the surface of a graft, seeded in a fibrin glue carrier. The difference in strength between the experimental and control groups was shown to increase over time after application of these cells up to eight weeks after surgery. This trend is in contrast with those observed for other interface healing enhancement materials. Histological examination showed the presence of type II collagen at the tendon-bone interface eight weeks after surgery. Histological characteristics of the interface were found to be similar to normal rabbit ACL insertions.[54] The development of insertion architecture comparable to that of the native ACL is desirable if it results in comparable strengths and loading responses in the graft.

4.4.1.3 Periosteum

The augmentation of intra-tunnel sections using periosteum has been proposed due to the osteogenic potential of periosteal cells and tissue. A number of studies [2, 60-61] have found improvements in intra-tunnel bone development and an increase in mean load to failure using this technique. A further study found that while the periosteum treated grafts displayed higher strength than the control grafts treated six weeks after surgery (see Table 4.2), the difference at 12 weeks was not statistically significant. An additional group of grafts in this study were treated with bone marrow in addition to periosteum. No statistically significant difference was observed in fixation strength six weeks after surgery. However, at 12 weeks an increase of 47% was observed.[55]

The harvesting process for periosteal tissue is fast, requiring only three additional minutes of surgery.[60] In animal models, the addition periosteal tissue to tendon grafts provided increased strength and resulted in a change of failure mode compared to controls.[3] This technique has the advantage of delivering autologous bone-forming cells to the bone tunnel. It is also possible that the presence of the layer of periosteal tissue in the tunnel provides some mechanical benefit in limiting the movement of the graft within the tunnel.

Tendon grafts remain the “gold standard” in ACL replacement, despite various artificial grafts which have been proposed over the last thirty years. Although ultimately these artificial grafts were not considered successful, useful information may still be obtained from attempts to encourage long term fixation by improving bone healing around them. The following section reviews additional means for improving graft fixation that has been employed when implanting artificial ACL grafts.

4.4.2 Artificial Grafts

Prosthetic grafts for ACL replacement have been available since the 1970s. Examples of the materials used for these devices include carbon, Gore-Tex, Dacron, polypropylene, and polyethylene terephthalate (PET). Generally, outcomes of these devices have been poor, leading to the withdrawal from the market of the vast majority of artificial grafts. Failure modes for artificial grafts have included intra-articular rupture, foreign body reactions and loosening, abrasion at the bone tunnel exit, failure of fixation and poor intratunnel healing.[12] Abrasion at the bone tunnel exit has been shown to be significantly reduced by chamfering of the corners of the bone around the tunnel.[1] A number of studies have considered the promotion of intra-tunnel healing in artificial grafts. For example, the Leeds-Keio ligament, a polyester mesh intended to act as a

scaffold for soft tissue repair, was fixed in place using bone plugs, replicating the BTB type autografts.[12]

Following disappointing outcomes for artificial grafts due to wear and abrasion, the inclusion of biological components to allow for graft remodelling has been the subject of several papers. In the native ACL, the primary zones of the natural ligament-bone insertion structure (ligament, fibrocartilage, mineralised fibrocartilage, and bone) are populated by different cell types. Spalazzi et al. recently developed a three-phase scaffold designed to mimic this interface.[62] This single structure was made up of a poly(lactic-co-glycolic acid) (PLGA) mesh for fibroblast and soft tissue culture, PLGA microspheres for the transition zone and sintered PLGA and bioactive glass for the bone section. The device is suggested for use as a graft collar in ligament grafts. It has been shown to support the growth of multiple cell types (seeded *in vitro*) when implanted subcutaneously in an animal model but is yet to be tested functionally.

Chitin is a biopolymer found in the exoskeletons of crustaceans and insects. It is considered to be a bioactive material. One study proposed the application of chitin as a means of improving the attachment of artificial ligaments. This *in vivo* study in a rat model showed that the application of chitin/chitosan to a polyester fabric significantly increases pullout strength and bone formation in the short term.[63] The pullout strength of the treated samples was found to be twice that of the nontreated polyester controls two weeks after implantation. The advanced bone growth is attributed by the authors to the bioactivity of chitosan, including its ability to promote osteoblast attachment and extracellular matrix production. However, images of the coated and control materials also demonstrate that coating the fabric significantly increases the surface area available for cell attachment and this may also play a role in the advancement of bone formation.

A study of bone ingrowth into Gore-Tex PTFE artificial ligaments suggested that the porosity of the graft fibres, which were 75% air by volume, was key to allowing bone ingrowth. This suggests that the provision of porosity for tissue ingrowth at the bone-graft interface should therefore be considered important when applying bulk materials within the bone tunnel. A stable fixation was found within the bone tunnels up to 18 months after implantation in an ovine model.[64] However, these ligaments were later removed from the market due to problems including loosening and synovitis, along with two documented cases of osteolysis.[65] The implications of these findings as well as those for CaP based materials are considered in the discussion section.

4.5 Discussion

4.5.1 Test Methodologies

Differences in methodology render direct quantitative comparisons between these studies complex. Results of biomechanical testing may be influenced by rates of extension, clamping of samples, and chosen angles of flexion. These are not standardised across the testing included in this review. The type of animals used is inconsistent, with rabbit, porcine, and canine models all being common. The number of subjects also varies in animal tests.[28, 51]

Time periods for mechanical testing range from two weeks to 52 weeks. The majority of studies last between six and 12 weeks. As the graft healing progresses, differences between treated groups and controls tend to change and do not always follow predictable patterns. Although differences are visible at 6 weeks and sometimes earlier, this may not be a predictor of increased strength later, as shown by the results of Wen et al.[30]

A change in failure mode may be considered a simple means by which to measure at what point the bone tunnel ceases to be the weakest point in the graft. The change in failure mode in biomechanical testing may be therefore considered a useful indicator of improvement over control procedures. It should be noted, however, that if the graft material degrades over time, the mode of failure may change even if the fixation strength has not increased. Examination of failed grafts for assessment of degradation is not commonly carried out.

The extent to which the observed improvements in animal models may relate to changes in outcome for the patient is unclear. Clinical studies regarding this type of application of CaPs are rare. The use of CaPs in resorbable screws, for example, produced improved results in animal models but did not induce a clear improvement in outcome for patients.

4.5.2 CaPs for Bone Tunnel Healing

Broadly, many of these strategies for the augmentation of bone tunnel healing in soft tissue grafts have been shown to have promising effects. All of the CaP-based materials were judged to have induced improvements in the biological structures forming in the bone tunnels during healing. The improvements included increases in bone mass and changes in the nature of the tissue forming in the tunnels. In the majority of cases, UTS increased (see Table 4.1), suggesting that the application of these materials increases fixation strength in the short to midterm. However, increases in fixation strength do not always introduce a change in failure mode compared to that observed in the controls. Longer-term studies are desirable in order to properly assess increases in fixation strength in ACL grafting and to provide more detailed information for the planning of clinical trials, through which the benefits of these treatments to the patient may be assessed.

With respect to both increases in fixation strength and changing the mode of failure, the application of CaPs has been shown to produce results comparable to, and in some cases better than, those obtained using materials whose application is more challenging (see Table 4.2).

When considering which technique to apply for the improvement of intratunnel bone healing, it is important to evaluate the complexity and cost of the method with respect to its efficacy in improving fixation. In the future, the development of devices facilitating the application of GCSF or mesenchymal stem cells, both of which have been shown to produce significant improvements in strength, may be desirable. However, for immediate improvement in bone tunnel healing, the application of existing CaP products such as bone cement seems to significantly improve fixation at a low cost and using a simple procedure and existing approved materials. CaP-based materials were shown to increase fixation strengths and advance healing at the tendon-bone interface. They are widely used biomaterials which are simple to apply and are likely to be among the least expensive of the proposed methods. They have a long-standing safety record and Good Manufacturing Practices (GMP) for them are well established.

The improvements in bone tunnel healing in ACL grafts fixed using CaP is usually attributed to their chemical composition. Bone mineral is a nonstoichiometric form of CaP containing additional elements such as silicon and magnesium. Although the exact properties of CaPs depend on the manufacturing processes used to obtain them, they are generally considered to be bioactive. There is insufficient evidence to show whether any particular phase of CaP is preferable in this application.

In addition to the changes in the chemical environment around the healing interface, the application of CaP in injectable or bulk form may offer mechanical advantages in ACL graft fixation. In order for tendon-bone interfacial healing to occur,

movement between the two faces must be limited. Where an extensible graft, such as a tendon graft, is inserted into the bone tunnel, the application of bone cement or porous blocks may provide additional fixation proximal to the joint space, limiting intratunnel movement of the graft and facilitating healing. The improvement of bone tunnel healing in this manner may also limit abrasion and wear of the graft due to the restriction of intratunnel graft motion.

While CaP-containing screws are commercially available and clinical evaluation is possible, the application of CaP cement in the bone tunnels does not appear to have been the subject of a clinical study. *In vitro* studies of the application of CaP cements in the bone tunnel have shown significant and consistent improvements in fixation strength and healing of bone tissue in and around the tunnels. This technique could be simply applied and merits further examination.

4.5.3 Application to Artificial Graft Materials

For the attachment of future artificial grafts, techniques proposed for use in biological grafts may also be of use. Artificial grafts offer the advantage of being able to design both the graft material and the bone-graft interface. Materials which are chosen for their ligament-like properties may be adapted for bone attachment by the application of CaP-based materials. The combination of CaP with PVA, a material which usually resists cell attachment, has been shown to improve its attachment to bone. These techniques for combining polymeric materials with CaP could be adapted to improve the attachment of an artificial ACL graft.

4.6 Conclusions

This review examines the hypothesis that the application of CaP can improve bone tunnel healing after ACL replacement. In general, ACL-bone tunnel fixation strength can be increased by approximately 100% through the incorporation of CaP and other

techniques. The application of growth factors and stem cells merits further investigation but is not immediately clinically applicable. The use of commercially available CaP cements induced changes in all the major indicators: bone formation, biomechanical strength, and mode of failure in biomechanical testing. While the evidence is not conclusive, it suggests that CaP materials perform as well as more complex biologic or cell-based solutions in this application. Studies show that the presence of CaP induces improvements in healing as investigated using histology and medical imaging as well as increases in strength and changes in mode of failure in mechanical testing.

A clinical study into its use to augment fixation and bone tunnel healing in ACL grafts is merited. More specifically, a study linking experimental fixation strengths in a suitable animal model to clinical outcomes in human subjects would be of great benefit, both in establishing the efficacy of this treatment and in helping to establish what parallels, if any, can be drawn between biomechanical testing in animals and clinical results.

4.7 **References**

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CHAPTER 5 Kinematic Evaluation of Anterior Cruciate Ligament Reconstruction with a Synthetic Prosthesis

5.1 Introduction

The anterior cruciate ligament (ACL) is one of the four major ligaments of the knee, coursing from a posterior position on the medial wall of the lateral femoral condyle to a more anterior position on the tibial plateau.[1] This orientation enables the ACL to function as the primary restraint to anterior tibial translation (ATT), maintaining proper relative tibiofemoral orientation and providing joint stability throughout the range of knee motion.[2-3] Additionally, the ACL is the secondary restraint to internal tibial and valgus rotational loads.[4] Collagen fibers in the native ACL are aligned along the ligament axis to bear tensile loading and exhibit a periodic crimp pattern resulting in a low-stiffness toe at low strains and increasing stiffness at greater strains as the collagen is straightened.[5-7] Several authors have suggested that the presence of the toe region may be important for the prevention of creep and fatigue, however, we were unable to find documented experimental evidence demonstrating this.[8-9]

ACL disruption is a relatively common knee injury with an incidence rate estimated to be approximately one out of 1750 in persons from 15 to 45 years of age in the United States.[10] The ACL has a poor intrinsic healing capacity due to a lack of significant vascularization in the adult; therefore, reconstruction is the recommended treatment for ACL rupture.[11-12] Currently, autografts and allografts are used for ACL replacement; however, drawbacks such as donor site morbidity and lack of availability still leave room for improvement.[12-13]

In the current study, a computational finite element model of the knee was built and validated. The model was then used to evaluate the kinematic behavior of a knee

reconstructed with an ACL prosthesis for comparison with the intact knee. Installation factors, specifically the tension at which the prosthetic is placed and the femoral tunnel orientation used, were evaluated to determine how they affect functional restoration.

Graft tension, generally determined by the amount of extension applied to the intra-articular section of the ligament-replacement prior to attachment to the bone, is known to be an important factor affecting knee function.[14-21] However, the precise value for the ideal tension for each combination of fixation and graft type has yet to be completely determined from empirical or clinical experience. Cadaver and short-term animal studies have indicated that low initial graft tension can result in joint laxity and irregular kinematics while high tension reduces laxity and can limit extension, cause posterior subluxion of the tibia relative to the femur, increase compressive forces on the articular surface, and accelerate joint degradation.[16, 19, 22-24] Most long-term *in vivo* studies have focused on biological grafts; however, the long-term behavior of frank replacement prosthetic devices, which are expected to retain their original properties *in vivo*, should differ since they do not remodel after implantation.[16] A prosthetic device may be subject to non-biological effects which occur prior to osseointegration, such as viscoelastic creep, fixation slippage, loosening, and fatigue; and if these are quantified, the relationship between initial and long-term tension and length may be extrapolated in a more straightforward manner than with biological grafts. Many types of fixation devices are successfully used to secure grafts to the femur and tibia without slippage and with sufficient strength and stiffness to support osseointegration and sustain loading during rehabilitation.[25] The present study focuses on the long-term case of a reconstructed knee in which a prosthetic ACL has already osseointegrated, forming a rigid attachment with the bone. The sensitivity to changes in tension were examined in terms of anterior laxity to define a range of acceptability for placement of the prosthetic.

In an ACL reconstruction, two common orientations in which the femoral tunnel can be drilled are (1) transtibially or (2) through an auxiliary anteromedial portal, with each method having advantages and disadvantages.[21, 26-28] Using the transtibial technique (TT), the femoral tunnel is drilled directly through the tibial tunnel with the knee flexed to approximately 90°. Transtibially placed biological grafts have been shown to be effective at restoring anterior-posterior translational stability; however, this technique places the tunnel more vertically and outside of the native ACL footprint, which some authors have associated with inferior rotational stability, particularly with regards to limiting internal tibial rotation.[27-28] Alternatively, the femoral tunnel can be drilled independent of the tibial tunnel through an auxiliary anteromedial (AM) portal adjacent to the patella with the knee flexed to 110° to 130°. Drilled from the anteromedial portal, the femoral tunnel exit lies within the footprint of the native ACL which may result in better rotational stability; however, this method is slightly more invasive, requiring the extra portal.[27-28] Controversy exists over which technique is superior, with the selection often coming down to surgeon preference and experience. In the current study, the two orientations were compared in terms of anterior laxity, rotational stability, and stress concentrations.

A prospective design for a prosthetic ACL may be a composite structure consisting of polyvinyl alcohol (PVA) and ultrahigh molecular weight polyethylene (UHMWPE) fibers. The design exhibits a ligament-like toe during extension which we hypothesize may be advantageous for the application of ACL replacement. The effect of the toe region was studied by comparing knees reconstructed with the non-linear prosthetic to the same with a hypothetical linear device. These reconstructions were compared in terms of anterior laxity and stress concentrations to determine if the inclusion of a toe was necessary or provided any advantages over a linear replacement.

5.2 Methods

5.2.1 Building the knee models

Magnetic resonance imaging (MRI) data of the fully extended right knee of a 41-year-old female was obtained from surgeons at Hôpital Bon-Secours in Metz, France. 3D Slicer v3.6, an open-source application for medical image computing, was used to build an anatomically accurate virtual model of the knee from the DICOM data.[29-32] The tibia, femur, fibula, and menisci, were outlined in each image layer and compiled to create a three-dimensional model of each structure. Additionally, the footprints of the anterior and posterior cruciate ligaments and medial and lateral collateral ligaments were noted from the MRI and marked on the virtual femur and tibia.

The bones and menisci structures were then imported as parts into a finite element computational mechanics model (Abaqus/CAE 6.9) and assembled in their correct relative orientation. ACL-intact and the ACL-deficient models were created as controls with which prosthetic reconstructed knees could be compared. The four ligaments were each modeled as dual-bundled structures, comprised of an anterior and a posterior bundle, consistent with anatomic and biomechanical observations.[1, 33] Each bundle was modeled as a single one-dimensional axial element with non-linear elasticity and initial strain values extrapolated from experimental data reported in the literature.[34-37] The centers of the footprints of each bundle were estimated from the MRI and selected as the attachment points. The bones were modeled as rigid structures and the menisci as linearly elastic solids with a Young's modulus of 59 MPa and a Poisson's ratio of 0.49 as in a previous study.[34] A pathway was imposed for passive knee flexion consistent with knee motion studies describing the normal range of relative displacement and rotation between the femur and tibia during flexion from 0° to 90°.[38-39]

Reconstructed knee models were created in which the ACL was replaced with a 9-mm diameter, cylindrical prosthetic ligament suspended between a femoral and a tibial tunnel. The mechanical behavior of the prosthetic was modeled using a Marlow hyperelastic constitutive relation fit to uniaxial tensile test data for the PVA and UHMWPE prosthetic. The prosthetic was divided into three sections along the length of the cylinder; a femoral tunnel section at one end, adjacent to an intra-articular ligament section in the center, and a tibial tunnel sections at the other end.

Tension was modified by extending or slackening the intra-articular section of the prosthetic prior to applying tie constraints to the bones, which were maintained in the same relative orientation in space. To simulate the reconstructed knee in the fully osseointegrated state, rigid tie constraints permitting no relative motion were applied between the bone tunnel walls and the outer surfaces of the sections of the prosthetic surfaces lying within the tunnels after the application of extension or slack. Tensions were reported with the knee at 30° flexion, an angle at which grafts are routinely tensioned and attached during reconstruction.[40-41]

Prosthetic reconstruction models were created with the femoral tunnels in two different orientations. The first orientation was with the femoral tunnel drilled transtibially with the knee at 90° of flexion, resulting in a more vertical placement at approximately the 11 o'clock position. The other orientation was a more lateral placement at approximately the 10 o'clock position consistent with a reconstruction in which the femoral tunnel is drilled from an auxiliary anteromedial portal adjacent to the patella with the knee at 130° flexion.

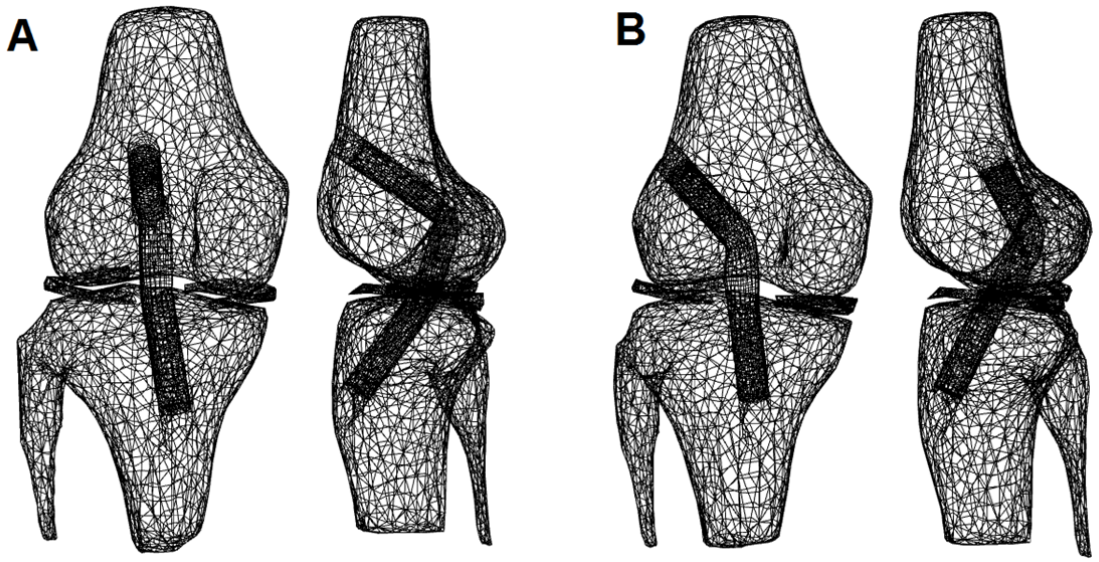

Figure 5.1 Coronal and sagittal views of transtibial (A) and anteromedial (B) reconstructions.

Reconstructions were evaluated kinematically and compared in terms of anterior laxity, rotational stability, and stress concentration. Anterior laxity was evaluated by measuring the amount of ATT in response to an applied 134-N (30 lbs) anterior tibial load as in the physical study by Yagi et al. to simulate a clinical evaluation with an arthrometer. [4, 40] Rotational stability was assessed by measuring the anterior displacement in response to 10-N·m valgus torque combined with 4-N·m internal torque applied to the tibia as to simulate the pivot shift test.[4] Simulated anterior laxity and rotational examinations were executed with the knee at 0° and 30° flexion with the femur held stationary. The evolution of stress concentrations within the prosthetic were evaluated over the course of the knee flexion from 0° to 90°.

5.2.2 Model validation

The model was validated by comparing outputs from the simulated ACL-intact and ACL-deficient controls against physical experimental data from the literature. The anteromedial bundle(AMB) and posterolateral bundle (PLB) length changes were

measured over the course of flexion to extension along with the resultant force generated within the ACL in response to passive knee flexion. The controls were also tested for anterior translational laxity and rotational stability and compared to physical experimental results from the literature.

5.2.3 Kinematic evaluations of reconstructed knees

The kinematic evaluation of knees reconstructed with the prosthetic ACL proceeded as follows. In Study 1, the objective was to determine if ACL primary function could be achieved using the prosthetic ligament in our model. For each femoral tunnel orientation, the tension of the intra-articular segment of the prosthetic was adjusted to determine if an acceptable fit to the anterior laxity of the intact knee could be achieved and to determine the ideal level of tension. Then, in Study 2, the sensitivity to changes in tension were examined in more depth to define an acceptable range for placement. The intra-articular aspect was extended and slackened in 1 mm increments up to 5 mm in each direction from the ideal tension found in Study 1 prior to attachment, with each perturbation tested for anterior laxity. Next, in Study 3, the effect of orientation was examined in more depth to determine if one orientation demonstrated any superiority over the other. Rotational stability and stress concentrations in the device over the course of the knee flexion from 0° to 90° were compared in prostheses installed at the ideal tension from Study 1 in the transtibial and anteromedial portal drilled femoral tunnel orientations. Finally, Study 4 focused on the effect of toe region by measuring the anterior laxity and stress concentrations on simulated reconstructions using nonlinear and linear prostheses. The stiffness of the linear material was selected as the average stiffness of the nonlinear material over the functional force range of the native ACL, from 0 N to 700 N.[42]

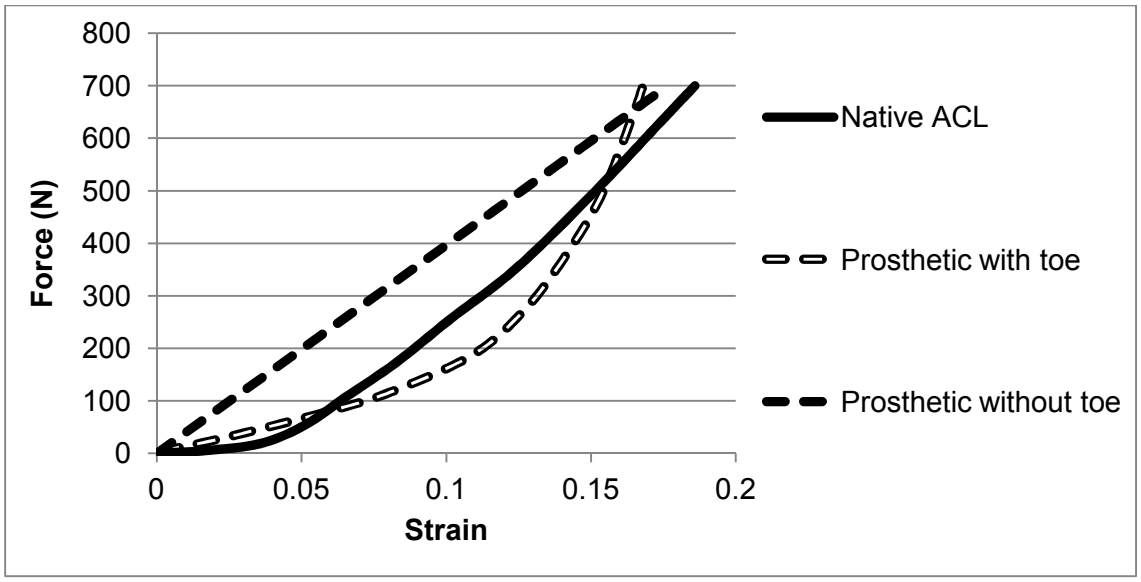

Figure 5.2 The single-axis force versus strain behavior for the nonlinear and linear prostheses tested shown alongside that of the native ACL.[1, 6] Curves are shown up to 700 N force.

5.3 Results

5.3.1 Validation

AMB and PLB length changes as well as ACL resultant forces over the range of flexion to extension were observed to fall within the experimentally determined normal range.[43-45] These measurements together provided assurance that the imposed knee motion, the locations of each of the ACL bundle footprints, and the initial strains in each bundle were anatomically accurate.

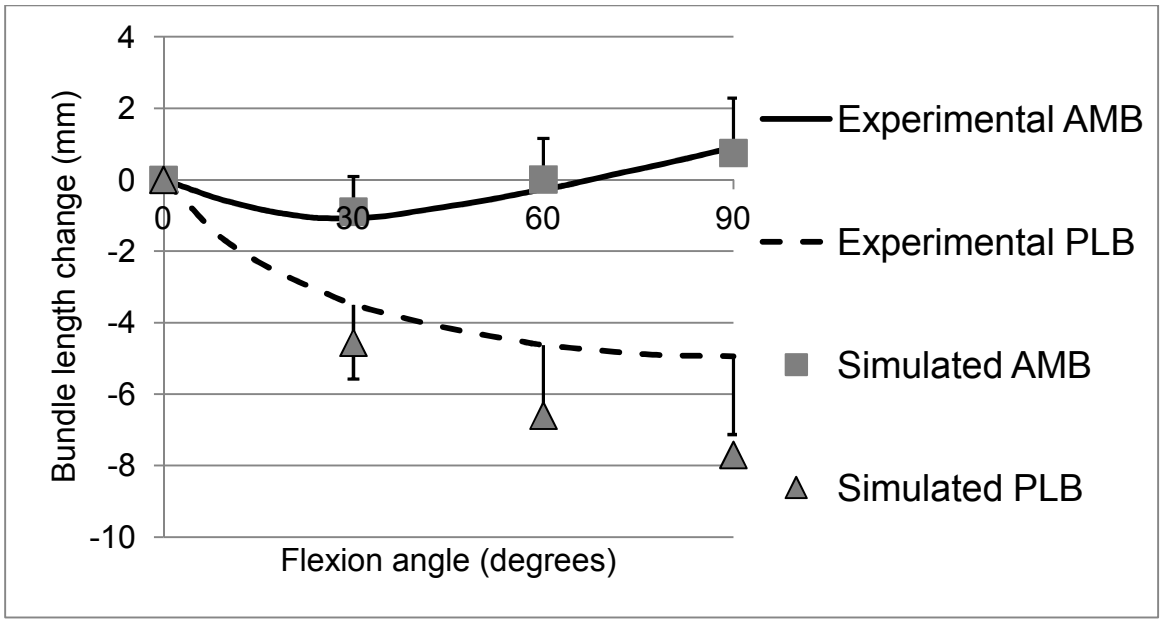

Figure 5.3 Simulated AMB and PLB length changes shown alongside experimental results from Amis and Dawkins.[43] Error bars represent one standard deviation for the experimental data.

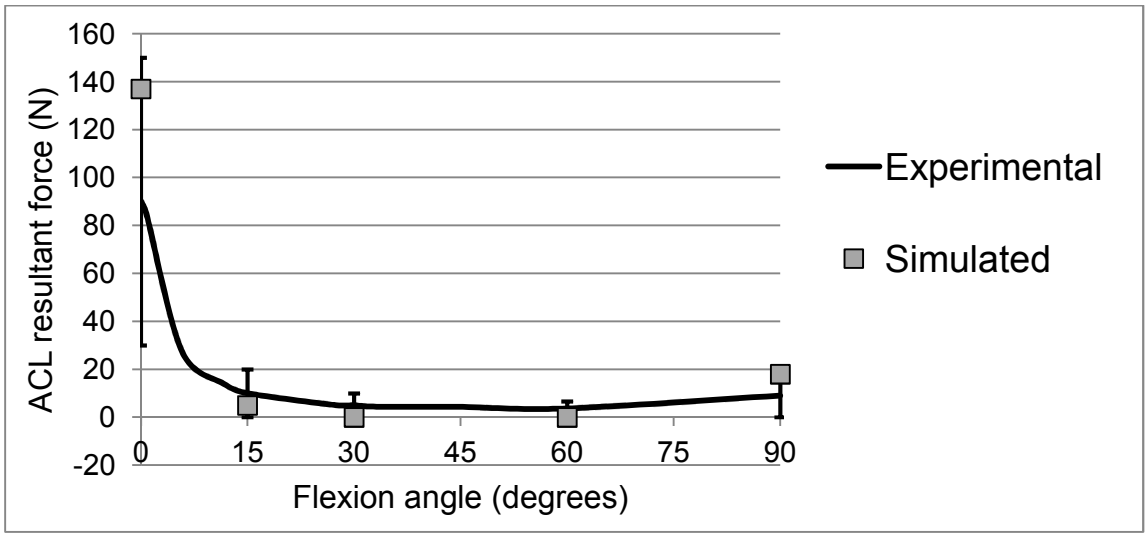

Figure 5.4 Simulated resultant force as a function of flexion angle shown alongside experimental results from Wascher et al.[44] Error bars indicate the approximate range of values reported from the experimental data.

ATT measured in the simulations on the controls were found to closely match with physical experimental data from a biomechanical study within one standard deviation as shown in Figure 5.5.[40] At 0° and 30° of flexion, the ACL limits anterior

tibial translation to approximately 5 mm and 7 mm, respectively. Without the ACL, translation increases to approximately 13 mm and 20 mm. The rotational behavior, evaluated with the simulated pivot-shift test on the controls was also found to produce the same trend as observed with the physical data.[4] As shown in Figure 5.6, in both the experimental and simulated results, ATT in response to combine rotary loading was greater in ACL-deficient and PLB-deficient knees and less in ACL-intact and AMB-deficient knees.[4]

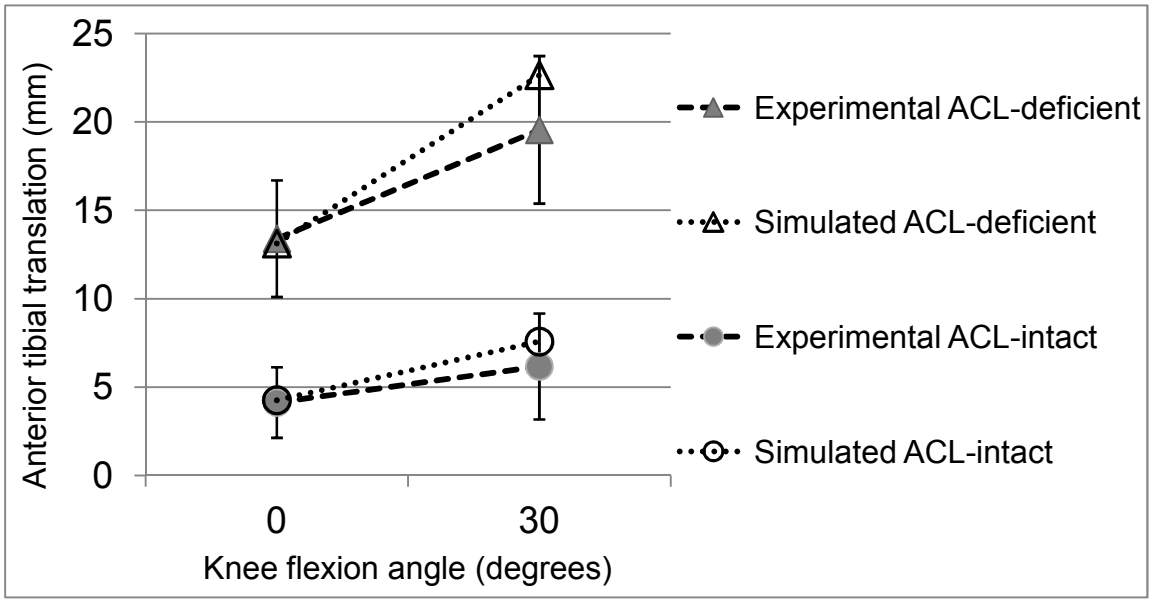

Figure 5.5 Simulation and experimental measurements of ATT in response to 134-N anterior tibial load applied to ACL-intact and ACL-deficient knees. Experimental results are shown as mean ± standard deviation from Yagi et al.[40]

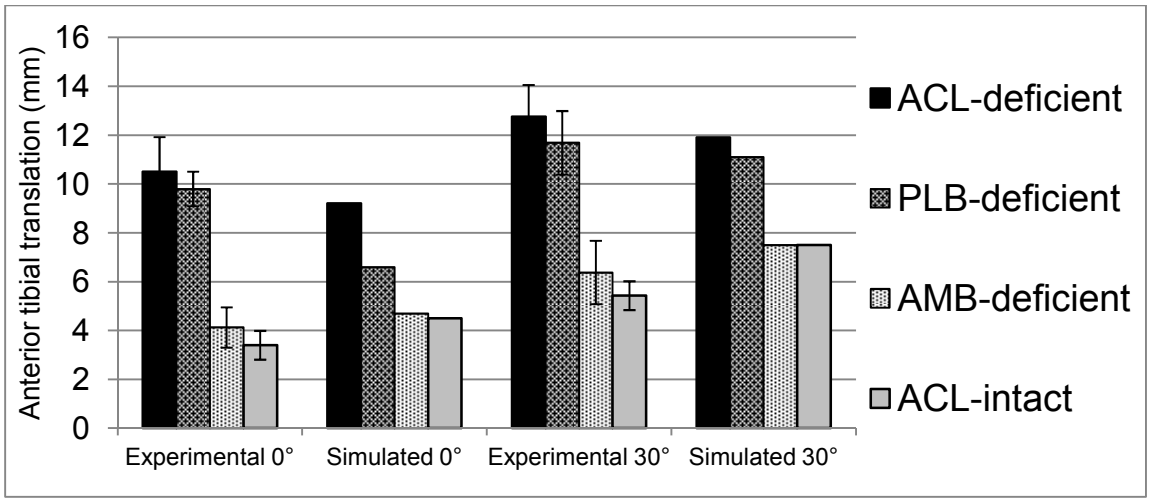

Figure 5.6 Simulation and experimental measurements of anterior tibial translation in response to combined rotary loading of 10-N·m valgus torque and 4-N·m internal tibial torque. Experimental results are shown as mean ± standard deviation from Zantop et al.[4]

5.3.2 *Study 1: Ideal tension for restoration of anterior laxity*

Anterior laxity close to the level of the native ACL could be achieved using the prosthesis in both the transtibial and anteromedial orientations as shown in Figure 5.7. For the transtibially oriented prosthetic, the ideal tension, that which most closely matched the anterior laxity of the native ligament, was found to be 10 N at 30° flexion. This level of tension was achieved by extending the prosthetic by 0.5 mm prior to bone attachment. For the anteromedially oriented prosthetic, the ideal tension at 30° flexion was found to be 0 N with no slack. The anterior laxity was very similar in both orientations and was not a distinguishing metric for comparison.

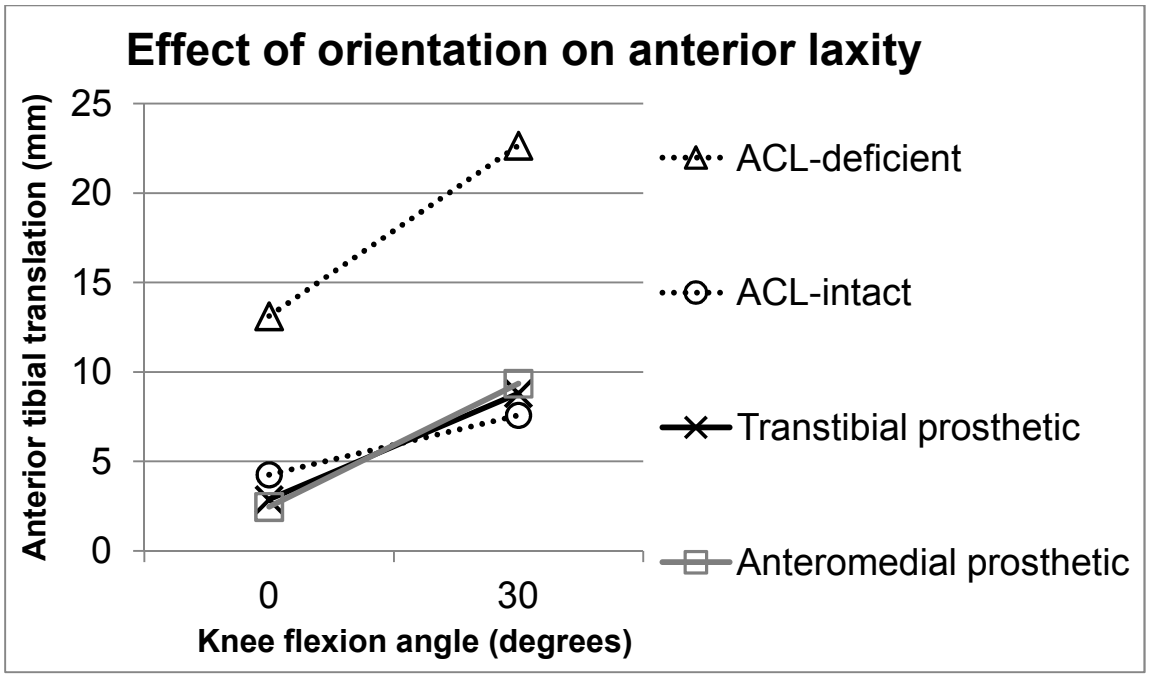

Figure 5.7 ATT in response to 134-N anterior tibial load in simulated transtibial and anteromedial prosthetic reconstructions with the ideal tension of 10 N for transtibial and 0 N for anteromedial implantations shown with simulated ACL intact and deficient controls.

5.3.3 *Study 2: Effects of changes in tension on anterior laxity*

In both orientations, tightening or loosening the device by up to 2 mm relative to the ideal level of tension found in Study 1 resulted in anterior laxity falling within approximately one standard deviation of the average intact knee or autograft reconstructions.[40] In the transtibial orientation, extending the device by 2.5 mm prior to attachment tightened the prosthetic to a tension of about 100 N at 30° flexion. Restoration of function was attainable with the graft installed with somewhere between 100 N of force in tension and 0 N with up to 1.5 mm of slack at 30° flexion.

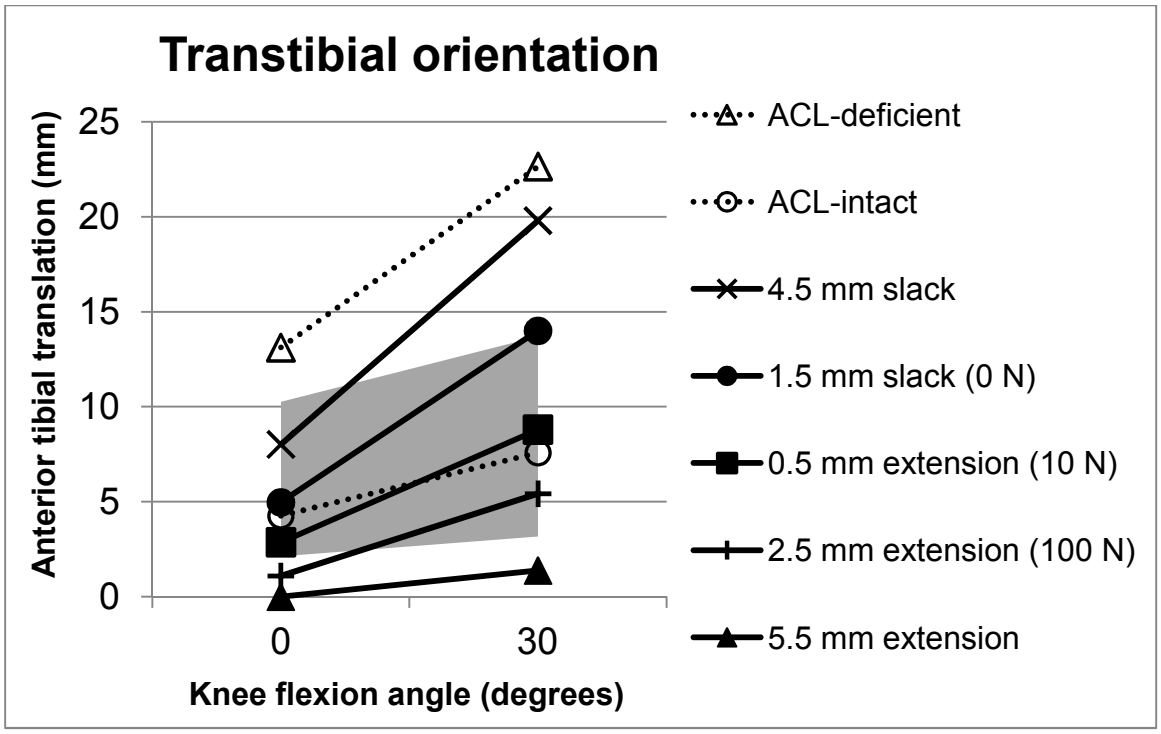

Figure 5.8 ATT in response to 134-N anterior tibial loading with prosthetics placed at varying levels of extension and slack in the transtibial orientation shown alongside simulated ACL-intact and ACL-deficient controls. The shaded area covers the range within one standard deviation of the intact knee and currently accepted ACL replacements from an experimental study by Yagi et al.[40]

Alternatively, in the anteromedial portal drilled orientation, the range yielding results within one standard deviation of currently accepted replacements was from an installation tension as high as 40 N to as low as 0 N with up to 2 mm of slack at 30° flexion. In general, installation of a graft with excessive tension results in over-constraint of the joint while excessive laxity results in knee instability.

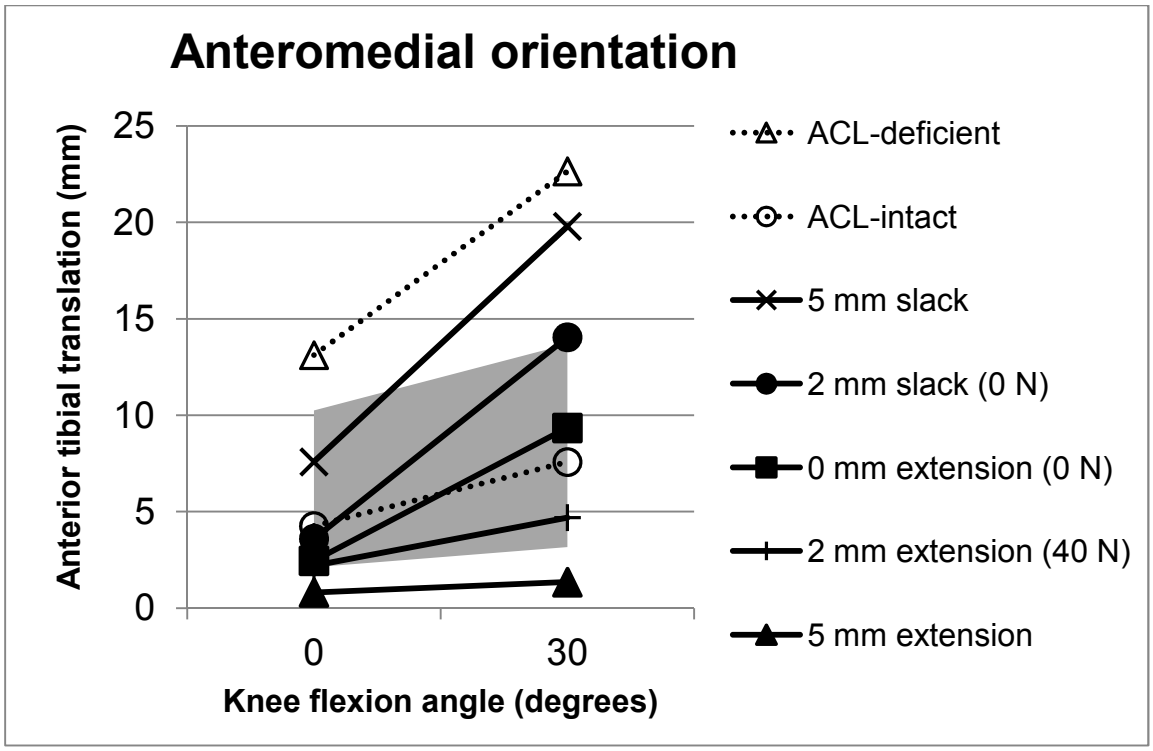

Figure 5.9 ATT in response to 134-N anterior tibial loading with prosthetics placed at varying levels of extension and slack in the anteromedial orientation shown alongside simulated ACL-intact and ACL-deficient controls. The shaded area covers the range within one standard deviation of the intact knee and currently accepted ACL replacements from an experimental study by Yagi et al.[40]

Table 5.1 Range of tensioning for prosthetic placement resulting in restoration of anterior tibial restraint within one standard deviation of the native ACL and currently used autograft reconstructions.[40]

Femoral tunnel drilling orientation	Maximum slack (minimum tension)	Ideal extension (tension) for placement	Maximum extension (maximum tension)
Transtibial	1.5 mm slack (0 N)	0.5 mm extension (10 N)	2.5 mm extension (100 N)
Anteromedial	2 mm slack (0 N)	0 mm extension (0 N)	2 mm extension (40 N)

5.3.4 Study 3: Effect of tunnel orientation on rotational stability and stress concentrations

The simulated pivot shift test confirmed previous reports that ACL replacements attached from anteromedial portal drilled tunnels provided greater rotational stability

versus transtibially oriented replacements.[27-28] As shown in Figure 5.10, the ATT in response to combined valgus and internal tibial torques was reduced by close to 2 mm, a decrease of 23% to 35%, using the anteromedial orientation.

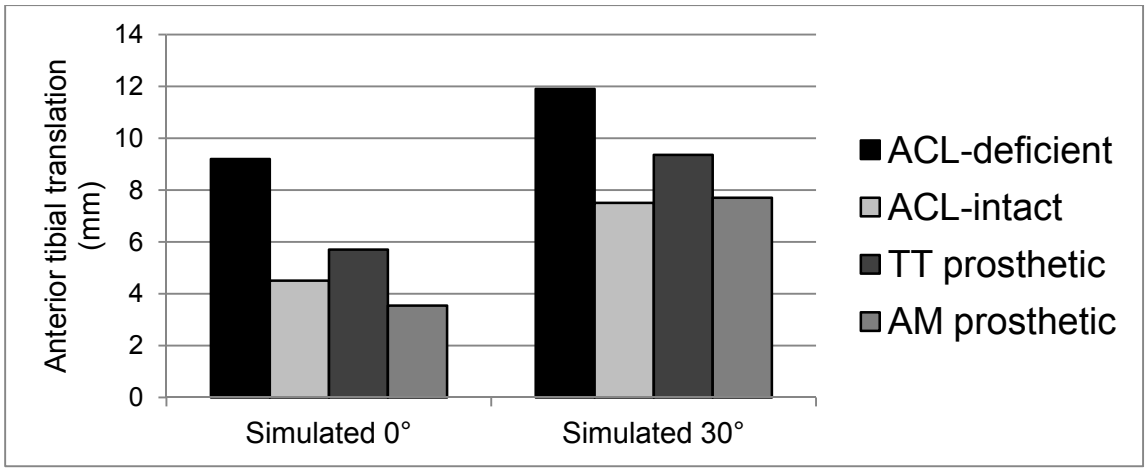

Figure 5.10 ATT in response to combined rotary loading of 10-N·m valgus torque and 4-N·m internal tibial torque on simulated transtibial and anteromedial prosthetic reconstructions shown alongside simulated ACL-intact and ACL-deficient controls.

At the ideal installation tension, the prostheses in both orientations were subjected to passive knee flexion from 0° to 90° to analyze and compare stress concentrations produced in the devices. In both orientations the greatest stress concentrations arose near the femoral tunnel exit with the knee at full extension. This was the angle of knee flexion and location along the length of the device where the prosthetic was subjected to the highest angle of bending. The greatest stress concentration occurred at the outermost radius of the bend. Maximum stress in the transtibial oriented prosthetic was found to be 29.5 MPa, almost 50% greater than in the anteromedial portal oriented prosthetic, measured as 20.5 MPa. The increase was also correlated with a greater prosthetic bending angle up to 90°, in the transtibially oriented device versus only about 60° for the anteromedially oriented device. At 30°, 60°, and 90° of knee flexion, the maximum stress in the transtibial device decreased to 12.0, 5.0,

and 4.8 MPa, compared to 6.9, 5.5, and 8.4 MPa in the anteromedial device, respectively. The maximum stress arising in either orientation was well below the ultimate strength of the prosthetic, measured experimentally as greater than 65 MPa, thereby indicating a low risk of rupture.

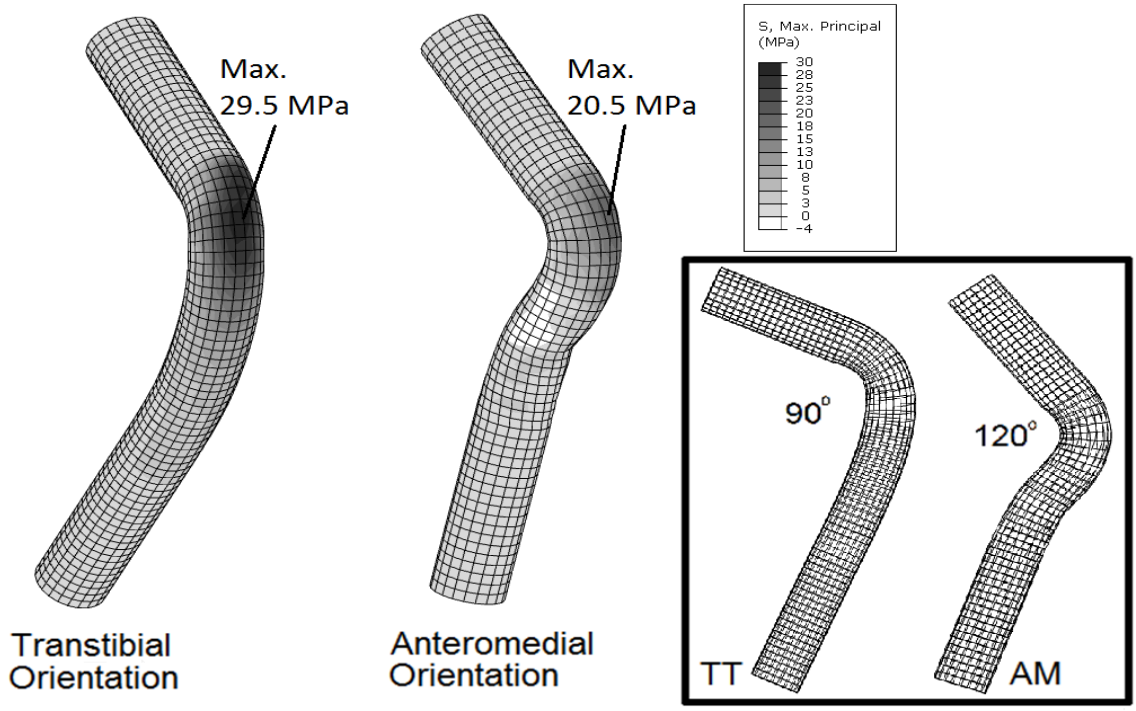

Figure 5.11 Maximum principal stresses in the device occurring at full extension in the transtibial (TT) and anteromedial (AM) orientations. Inset shows maximum prosthetic bending angle in both orientations, which occurred at full knee extension.

5.3.5 *Study 4: Effect of toe region presence*

The presence of the low stiffness toe at low strains was evaluated to determine if this nonlinearity in the mechanical behavior of the prosthetic ligament provided any advantage over a device with linear elasticity. In both orientations, the placement tension of both the linear and nonlinear prostheses could be adjusted such that restoration of anterior laxity close to the native ACL could be achieved; therefore, primary function was not a distinguishing feature for evaluation of toe presence.

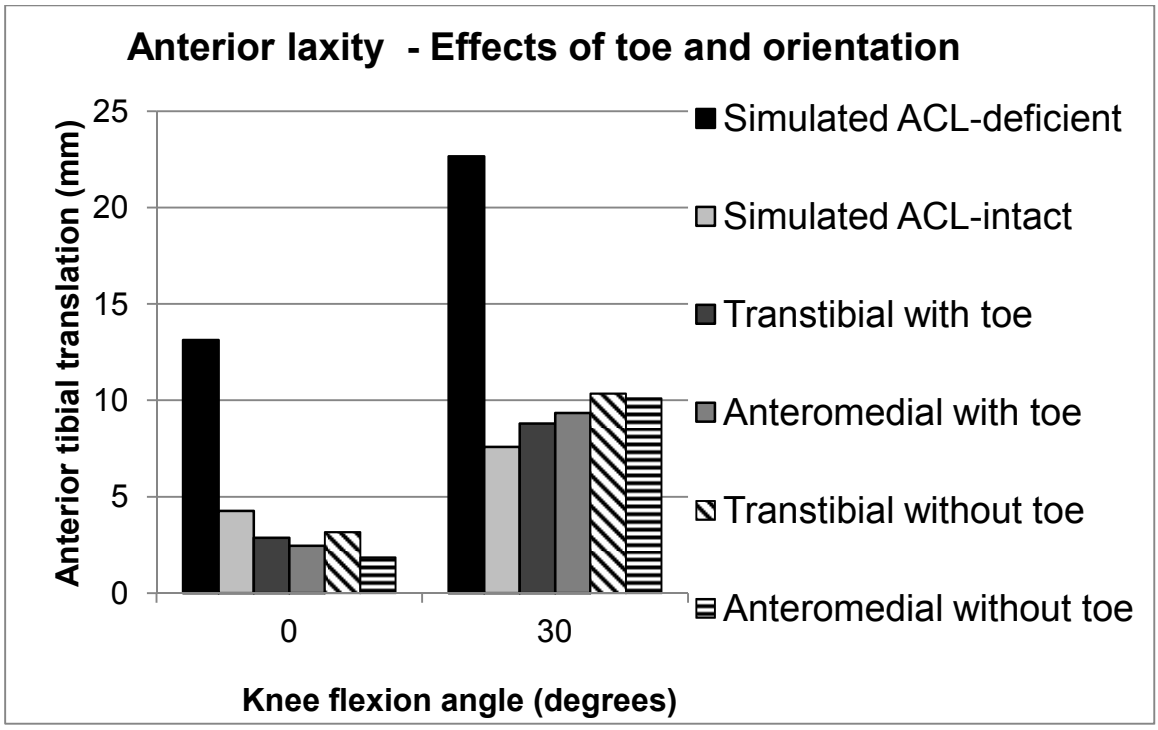

Figure 5.12 Simulated results comparing ATT produced in response to a 134-N anterior tibial load in knees reconstructed with linear and nonlinear prosthetic ACL. Results are shown alongside simulated ACL-intact and ACL-deficient controls.

Differences were observed in the stress concentrations in the prosthetics as the knee was flexed from 0° to 90°. In both implant orientations and at all tested flexion angles, the presence of the toe region was found to reduce the maximum principle stress from as little as 10% to as much as 200%. The greatest maximum stress incurred over the range of flexion consistently arose at full extension. Toe presence reduced the maximum stress at full extension by about 10% in the transtibial orientation and 30% in the anteromedial portal drilled orientation. This reduction in stress would provide an advantage in terms of prolonging the fatigue life of the structure, demonstrating that nonlinearity, specifically the presence of a low stiffness toe at low strain, would be a desirable feature for an ACL prosthetic.

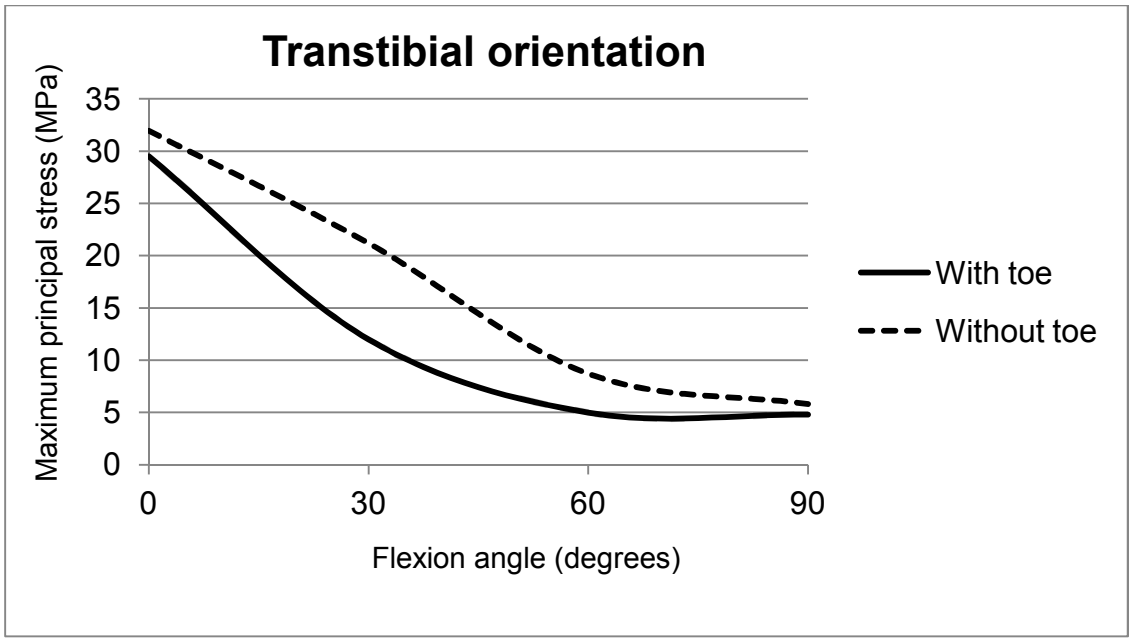

Figure 5.13 Maximum principle stresses arising in linear and nonlinear prosthetics in the transtibial orientation over the range of knee flexion from 0° to 90°.

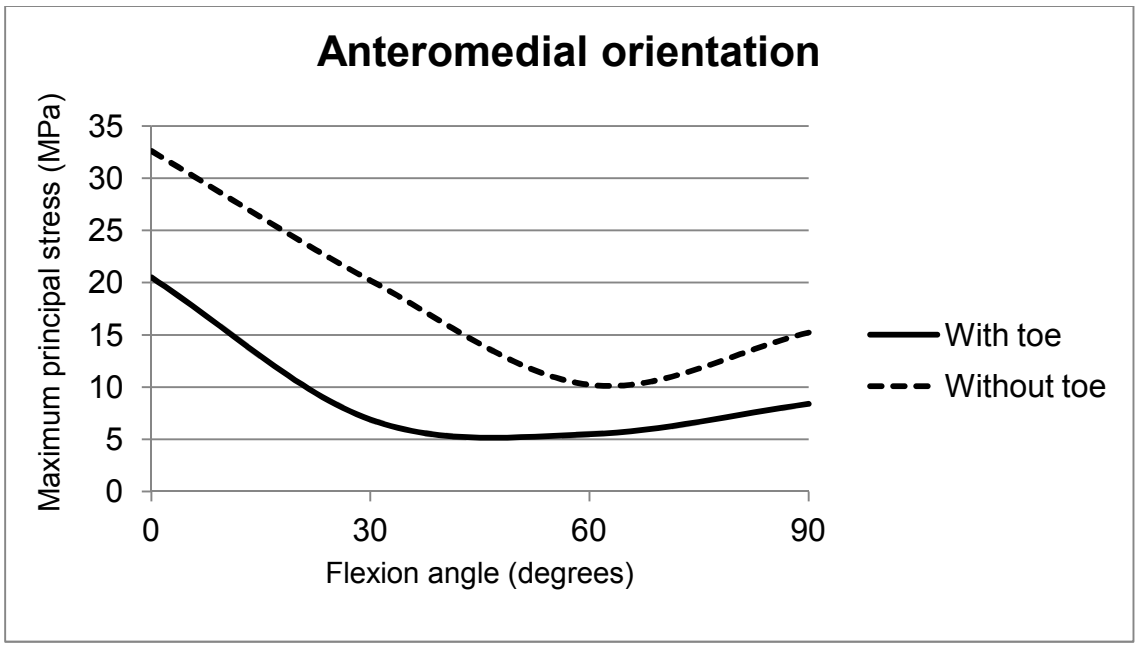

Figure 5.14 Maximum principle stresses arising in linear and nonlinear prosthetics in the anteromedial orientation over the range of knee flexion from 0° to 90°.

5.4 Discussion

The kinematic simulation used here demonstrated that a non-linearly elastic prosthetic possesses adequate mechanical properties to restore primary ACL function. With the device installed at the ideal tension, anterior tibial restraint was similar in the transtibial and anteromedial portal drilled tunnel orientations, with both capable of providing a close match to the native ACL. Ideal tension for the transtibially oriented graft was found to be 10 N, slightly greater than the ideal value of 0 N for the anteromedially oriented graft; however, several millimeters of deviation either way from the ideal resulted in acceptable restoration of anterior tibial restraint similar to the currently used grafts.

Though both orientations were similar in terms of resistance to anterior tibial loading, differences emerged upon assessment of rotational stability and stress concentrations. The anteromedially oriented prosthetic was found to provide better rotational stability, a result consistent with previous physical experiments on reconstructions with biological grafts.[4, 28] Additionally, the maximum stress within the device was significantly lower using the anteromedial orientation than with the transtibial orientation. Taking into account only these measures, the anteromedial portal drilled orientation performed better; however, the transtibial orientation was still acceptable in terms of kinematics and may provide procedural or other advantages not herein addressed.

With regards to the design of the mechanical behavior, the inclusion of a low stiffness toe region at small strains, as observed with the native ACL, was shown to be advantageous. Relative to a purely linearly elastic ACL replacement, the presence of a toe region reduced stress concentration during knee motion while providing the same

level of function in terms of anterior laxity. Greater stresses would theoretically increase the rate of fatigue and shorten the service life of the device.

Several finite element analyses have been used in recent years to kinematically evaluate different aspects of ACL reconstruction. The earliest reported was a study by Suggs et al. in 2003 in which grafts of varying stiffness corresponding to the ACL and bone-patellar tendon-bone grafts were installed at two levels of tension and compared in terms of anterior laxity. In that study, the grafts were modeled as nonlinear springs providing no information on stress concentrations.[46] A finite element study by Au et al. focused on the stress concentrations in the bones and how they were affected by tunnel placement.[47] Peña et al. evaluated the effects of the stiffness of bone-patellar tendon-bone, gracilis, and quadrupled semitendinosus grafts and initial graft tension on anterior laxity and stress concentrations using continuum models for the grafts.[48] A later study by the same group also compared tibial and femoral tunnels drilled at different angles also in terms of anterior laxity.[49] Rotation (though not translation) was evaluated in one finite element analysis by Ramaniraka et al. which compared single bundle, double bundle, and extra-articular reconstructions.[50] Some distinguishing features of this study compared to previous simulated kinematic evaluations include the new material behavior of the PVA and UHMWPE prosthetic, the evaluation of the prosthetic with the toe versus the prosthetic with linear behavior, and the evaluation of stress concentration and rotation in transtibial and anteromedial drilled tunnel orientations. Anterior translation, rotation, and stress concentrations were evaluated together to give a more complete understanding of the kinematic and functional effects of each variation.

The simulation had several limitations related to the differences from the *in vivo* case introduced with the simplifications and assumptions made when building the model. The models were created to simulate the fully osseointegrated case by applying rigid tie

constraints between the bone tunnels and the outer surfaces of the sections of prosthetics lying within the bone tunnels. Therefore, events occurring prior to full osseointegration and any relative motion between the bone tunnel and tunnel sections were not modeled. For example, in the immediate post-operative term, the prosthetic is secured to bone tunnels using one of the many types of initial fixators which vary widely in terms of size, placement location, securing method, pullout strength, and stiffness.[51-52] In the early stages, the restraint provided by an ACL replacement might not be constant due to several factors including changes in fixation and bone properties, graft healing and viscoelastic effects, as well as the progression of osseointegration, which were not accounted for in this study.[14, 53] These changes obfuscate the relationship between the initial graft tension and the long-term post-osseointegration tension evaluated in the study. To reconstruct the ligament in a manner in which the ACL replacement is tensioned to the level evaluated in this study, it might be necessary to apply greater tension at the time of installation. The amount of over-tensioning required would be dependent upon the aforementioned changes and has yet to be quantified.

The tie constraints and how they were applied between the bone tunnel and prosthetic had an effect on the results. For example, the shape of the bone tunnel exit may have bumps or irregularities that would directly affect the stress concentrations around the contact location on the prosthetic. The tunnel exit shapes should have some degree of variation with each patient including the patient from which the current model was derived; therefore, stress concentrations arising due to bone tunnel exit shapes were noted as such and not modeled. Regardless, it was observed that while some stresses arose at the bone tunnel edges, they were small relative to the peak stress concentrations arising from the imposed bending reported as the significant finding in the study.

Another limitation of the study was the modeling of the prosthetic as a single solid cylinder. A more realistic and ligament-like design might be a fibrous structure consisting of many smaller filaments. The stresses arising due to bending in a single larger radius cylinder are greater than in a construct of individual smaller cylinders since the stress increases with the distance from the neutral plane within each cylinder. Therefore, the value reported for the stresses are numerically representative of a solid cylindrical prosthetic; however, the results are still useful and valid for comparing relative stress concentrations in devices with different insertion techniques.

5.5 Conclusion

The kinematic model demonstrated that the prosthetic was capable of restoring the primary function of the ACL in either orientation when installed within a specific range of tension. Additionally, it was shown that installation using the anteromedial orientation resulted in better resistance to rotational loading and reduced stress concentrations. Finally, it was also shown that toe presence reduced stress concentrations. The computational results obtained provide evidence for the potential of a non-linearly elastic prosthetic as a promising alternative to biological grafts currently used for ACL reconstruction, giving some justification for further investigation.

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CHAPTER 6 Conclusion

6.1 Summary and significance

Each year, approximately 175,000 ACL reconstructions are performed in the United States, at a total cost exceeding $2 billion.[1-3] Biological tissue grafts are the current standard replacement option used for ACL reconstruction and have generally been successful at restoring knee stability and enabling patients to return to normal levels of activity.[4-6] Regardless, persistent problems including pain and loss of function at the donor site when using autografts and disease transmission risk, increased knee laxity, and lack of availability with allografts would make a prosthetic alternative advantageous.[6-9] Additionally, a prosthetic alternative would eliminate the need for the harvest operation for autografts and the need for procurement of allografts which would, in turn, provide significant savings in terms of operation times and costs.[9]

Several prosthetics have come and gone over the past 30 years; however, design insufficiencies have prevented these devices from gaining widespread acceptance.[6] Problems with past devices include lack of biocompatibility and generation of immunogenic wear particulate as well as susceptibility to creep and fatigue several years after implantation.[6] New biomaterials, improvements in orthopedic surgery, and better understanding of knee biomechanics may enable a next-generation prosthetic that is suitable for ACL replacement.

Design control concepts were applied in our attempt to develop a functional prosthetic ACL. Comprehensive design inputs were specified consistent with the demands of knee joint, with performance at least to the level of currently accepted replacements, taking into account the failure modes of previous devices. A risk analysis was performed and appropriate verification tests were devised to ensure safety and

efficacy. A design with several unique and novel features was developed and subjected to verification testing.

The proposed design is a composite structure consisting of polyvinyl alcohol (PVA) and ultrahigh molecular weight polyethylene (UHMWPE), with two tunnel sections to be placed in the bone tunnels on each side of an intra-articular ligament-replacing section. PVA and UHMWPE were selected based upon a good record of biocompatibility as well as mechanical strength and stiffness suitable for ACL replacement.[10-13] The rope pattern designed for the intra-articular section consisted of 12 UHMWPE threads braided around a core of 16 PVA cords with a helix angle between 40° and 50°. The structure had strength double that of the native ACL and greater than earlier devices such as the Dacron, Leeds-Keio, and ABC prosthetic ligaments, which were susceptible to failure from rupture *in vivo*.[6, 14] The design provided stiffness within the range of the native ligament and currently accepted replacements over the physiologically relevant force and strain range.[15-17] A novel feature engineered to extend the fatigue life is the presence of a low stiffness toe at low strain as observed with the native ligament.[18-19] Toe region presence was shown in a kinematic simulation to reduce stress concentrations over the course of knee flexion. The design was physically tested for fatigue and creep and performed satisfactorily up to 1 million cycles at which point testing was stopped.

The tunnel sections were designed with several novel features to support early fixation and optimize conditions for long term osseointegration. Porosity allows for bony ingrowth while a tubular shape allows full circumferential contact between the device and the tunnel and provides an open space inside the tube for placement of a screw fixation at the aperture or addition of osteoinductive substances such as calcium phosphates, growth factors, or bone mulch. The addition of loops at the far ends of the tunnel

sections enables compatibility with suspensory fixations such as buttons, crosspins, and staples providing more implantation options for the surgeon. PVA is hydrophilic and can swell in the tunnel improving the fit by increasing pressure against the bone tunnel wall. A coating containing calcium phosphate or another osteoinductive material may be applied to the outer surface of the tunnel sections to promote bony incorporation and healing.

An innovative computational kinematic evaluation tool was developed and validated in order to assess functionality of the device in the knee and determine the effects of placement tension and femoral tunnel orientation. Common clinical knee diagnostic assessments were simulated including the anterior drawer test and the pivot shift test to measure outcomes in terms of anterior laxity and rotational stability. The device provided good restraint to anterior tibial translation in both the transtibial and anteromedial portal drilled tunnel orientations; however, the anteromedial portal drilled orientation provided superior rotational stability and reduced the maximum stress. The tension at which the device was placed was found to be a critical factor for functional restoration, with a window of about 4 mm of extension providing results in line with the currently used grafts.

The reviews and studies presented in this thesis were performed to look at each of the major aspects of the problem of how to develop a prosthetic ACL and gather adequate preclinical data to assess feasibility, safety, and efficacy to support the progression to the next stage of *in vivo* testing. The results of the performed *ex vivo* verification and validation tests indicate that the composite PVA and UHMWPE design satisfies the critical design inputs and may be a promising alternative to biological grafts warranting further investigation.

6.2 Alternative solutions

In addition to the specific functional design upon which we have converged, it may be worthwhile to note other alternative design directions which may have also led to workable solutions. Materials selection was based upon a demonstrated history of biocompatibility and high tensile strength to avoid the observed failure modes of previous devices. Metals such as titanium or other polymers such as polyurethanes also demonstrate good biocompatibility and could perhaps be substituted for the UHMWPE with quantity adjusted to provide adequate strength. The advantages of hydrophilicity and the ability to swell in the bone tunnels might be provided by another material other than PVA; however, most other hydrogels with a history of implantation possess inferior strength or have been observed to degrade *in vivo*.

Additionally, the choices with regards to rope design are inexhaustible, possibly involving a combination of pattern types, hierarchical arrangements, and geometrical parameters. The braid type for the current design was selected based upon the comparison of several simple types of patterns and the application of general rope design principles, yet it is possible that some other pattern may also be capable of reproducing a ligament-like tensile response. However, it is also worth noting that more complex patterns with more points at which strands crossing over each other are usually more susceptible to wear damage and have inferior fatigue life.[20]

Other variations are also possible using the same materials and rope pattern as the current design. For example, more yarns of UHMWPE, each with a smaller diameter, or fewer yarns, each with a greater diameter could have been used. These changes may have an effect on the static and long-term behavior of the construct, but were not studied in the mechanical design analysis since a satisfactory result had been attained.

6.3 Limitations

There were several factors limiting certain aspects of the design and evaluation process. All the samples created for testing were braided or twisted in different patterns by hand with nothing more than a braiding disk and were, therefore, not as uniform as they would have been if manufactured with a braiding or winding machine. Additionally, one of the challenges associated with the fatigue study was the requirement that the samples remain submerged under water for the duration of the test as cyclic loading was applied and force and strain were recorded. Large clamps or capstans capable of gripping the full size samples could not fit inside the cylindrical chamber used to contain the water; therefore, smaller samples with only half the quantity of PVA were tested. A larger test chamber would enable better gripping for testing of full size samples. Time constraints limited testing to one million cycles, leaving the number of cycles to failure yet to be determined. Additionally, the long-term tests were only performed in tension, leaving other potential degradation modes such as bending and abrasion to be evaluated in a future study.

The kinematic evaluation had to be simplified due to incomplete knowledge of the biomechanical behavior of the knee. The most important structures contributing to knee kinematics, the collateral and cruciate ligaments and menisci, were included in the simulation and modeled with anatomically accurate attachments, tensile behavior, and initial strains defined using biomechanical data from the literature. Other structures were not included such as the patellar tendon and patella, the joint capsule, and the muscles, since they had similarly been neglected in earlier models and data regarding their behavior and effect on knee kinematics were more variable, less significant, and underdefined in the literature.[21-24] The model was validated using several different kinematic measurements to provide assurance that the simulated tests would provide

meaningful results. Nevertheless, more complete physical data would be required to build and validate a more robust model with a confidence level great enough to predict behavior at a wider range of knee flexion angles and in response to more complex loading conditions. Another weakness of the kinematic study was the fact that only one knee was used to create the model. Several orthopedic surgeons who routinely perform ACL reconstructions examined the model and assured that the knee was typical with no abnormalities, yet an averaged model from several knees may have been superior. Better yet, multiple models created from a range of knees would be useful to assess variability of the results.

6.4 Future directions

The preclinical benchtop and simulated verification results obtained support the feasibility of the composite prosthetic ACL. Long-term cyclic loading tests, monotonic creep tests, and cyclic bending tests should be executed using video strain measurements to acquire a better quantification of the elongation to expect *in vivo*, separated from the effects of clamp slippage. Design inputs which have yet to be evaluated with benchtop testing include bending fatigue and abrasion. For bending fatigue testing, the FDA recommends imposing combined bending and loading typical of normal activity which might vary depending on the tunnel orientation.[25] Abrasion testing, utilizing cadaver bone or different grades of abrasive material, can be combined as a part of the bending fatigue test by simulating the conditions at the attachment sites and places on the device where rubbing against the bone is likely occur.[25] Although a design has been envisioned and proposed for the tunnel sections, it may require additional engineering and verification testing of fixation strength and stiffness using cadaverous bone.[25] Cyclic loading might also be applied to determine if the fixation is susceptible to loosening.

Additionally, the FDA requires data to ensure that the device does not present adverse toxicological effects. This may be provided from prior clinical usage history and component toxicology information from the literature or with preclinical biological testing. Hazard identification information should be provided from tests for pyrogenicity, hemolytic potential, acute toxicity and intracutaneous irritation, cytotoxicity, genetic toxicity, and immunological potential.[25]

Next steps would include animal and clinical studies. Humans are the only species that is both bipedal and plantigrade; therefore, from a biomechanical standpoint, the human knee is unique and has no ideal animal model for assessment of functional restoration.[26] Regardless, the FDA recommends animal studies to assess histological and immunological reaction to the device and particulate, material degradation, abrasion, damage, particulate migration, fixation strength, and fibrous ingrowth.[25]

A first-in-man study would yield additional information regarding osseointegration, functional restoration, and implant survivability in humans. Factors lowering risk include the demonstrated biocompatibility of the constituent materials and the fact that in the case of mechanical failure, the device could be surgically removed and secondary replacement would be possible with a biological graft. In the United States, a first-in-man study, like other clinical trials, requires approval of the investigational plan by an Institutional Review Board (IRB) and an Investigational Device Exemption (IDE) approval from the FDA which is based upon adequate preclinical data. In Europe, first-in-man studies can commence with the approval of a local Ethics Committee (EC) and upon notification of the National Authority. Prosthetic ACLs have been classified by the FDA as a Class III medical device requiring full premarket approval (PMA) based upon proven safety and efficacy prior to market entry.[25] From a clinical standpoint, the availability of a reliable prosthetic alternative to biological grafts would reduce operation times,

accelerate the recovery period, and improve outcomes by the preclusion of donor site morbidity, thereby providing significant advantages for both patients and surgeons.

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APPENDIX

International Patent Application – Submitted January 20, 2012

PCT / EP2012 / 050917

DEVICE FOR TISSUE REPAIR

FIELD OF THE INVENTION

The present invention relates to a hydrogel based device for use as tissue repair.