Editorial

Future trends in ACL rupture management

1. Introduction

Injury to the ACL and the high frequency of subsequent knee instability, which can result in further damage to the joint, is more commonly diagnosed. There is a need to develop ACL substitutes with high initial strength and rigid fixation, which allowed immediate mobilization and the potential early return to athletics. Many materials were trialed; the major ACL prostheses considered at that time were poly-tetra fluorohydrate (Gore-Text), polyester (Dacron), carbon fiber, and polypropylene. Problems relating to wear and a lack of directed host tissue response leading to early failure were identified with each of these materials. Simultaneously, advances in arthroscopic and endoscopic ACL surgical techniques incorporating autologous tendon grafts, as well as dramatic advances in both fixation and rehabilitation, reduced surgical complications. Allogenic grafts also became a viable alternative as problems with secondary sterilization and tissue handling were recognized and overcome. In this first decade of the new century, our ability to manipulate biology and to promote healing of the injured ACL, as well as the advancing field of tissue engineering gives an opportunity for the development of an ACL graft, which may supplant current autologous techniques.

2. ACL reconstruction options

More than 200,000 ACL ruptures occur in the United States each year.¹ Autologous tendon grafts harvested at the time of reconstruction are the most widely utilized ACL replacement tissues, but result in tendon donor site morbidity. Allograft tendons have gained acceptance because there are no problems with donor site morbidity, but the cost and risk of infection and disease transmission remain as concerns. Although there have been excellent clinical results with these biologic sources, the transplanted tendon does not become histologically identical to the native ACL and, therefore, does not completely recreate the ACL's function.^{2–4}

3. Autografts

Sources of autografts include the bone-patellar tendon-bone (BPP), hamstring, and quadriceps tendons. BPP grafts have consistently provided excellent stability. Biomechanically, the BPP tendon is stronger (2900 N) and stiffer (685 N/mm) than the native ACL.⁵ Fixation with interference screws within the bone tunnels provides an initial pull-out strength of 640 N with rapid bone-to-bone healing.⁶ This fixation exceeds the 454 N that Noyes

et al.⁵ calculated as being necessary for normal physical activity, the results in a graft that closely approximates the physiological length of the ACL. BPP tendon autografts examined in an animal model initially weakened to 12% of the maximum load of the ACL 6 weeks following surgery, but regained 61% of the strength 6 months post-operatively. It should be noted that the initial strength of the BPP tendon grafts used in this study may have been significantly less (by as much as 50%) than the control ACL.⁷ Donor site morbidity remains the most common limiting factor of BPP tendon grafts. Anterior knee pain, sensory deficits, kneeling pain, patellar tendinitis, patellar fractures, quadriceps atrophy, and a large incision are commonly reported and can interfere with return to pre-injury athletic activities.^{12–14} Most surgeons protect the graft by reducing physical activity for 6 months before a return to athletic competition. This promotes recovery of quadriceps tone and strength, allows bony tunnel in growth, and enables the graft to regain the majority of its initial strength. Over time the graft incorporates into the bone tunnels, resynovializes and revascularizes intraarticularly, and provides long term stability in approximately 95% of patients (less than 3 mm anterior side to side difference).^{13,15,16} Despite static stability, only 80–85% of patients return to International Knee Documentation Committee (IKDC) level I and II activities (jumping, pivoting sports, basketball, football, soccer, skiing, tennis and hard labor).^{13,15,17} Hamstring reconstruction with double and quadrupled semitendinoses and gracilis tendon has gained popularity as a result of decreased graft harvesting morbidity and smaller incisions. Biomechanically, double (DS) and quadrupled (QT) tendons have superior strength (DS 2600 N, QT 4090 N) and stiffness (DS 534 N/mm, QT 776 N/mm) compared with BPP tendons and the native ACL.¹⁸ Fixation remains an issue with hamstring grafts. Interference screw fixation can cause graft damage and pulls-out at 200–350 N,⁶ which is less than the 454 N⁵ of forces associated with normal activity. Fixation with Endo-Button[®] on the femur has a pull-out strength of 628 N⁶ but is associated with bone tunnel expansion.¹⁹ Tibial fixation with staples or screws provides excellent pull-out strength (790–905 N),⁶ but the hardware prominence is often painful and requires removal. The graft heals into the tunnels via fibrocartilage; calcified fibrocartilage becomes fully incorporated in approximately 8 weeks.³ Intra-articularly the graft synovializes and revascularizes similarly to other autogenous grafts. Surgeons typically protect the graft 6 months to allow for graft maturation. Donor site morbidity is limited to infrequent saphanous nerve injury and hamstring weakness. The long term results of hamstring grafts have been reported with joint stability of approximately 90%; 75% of patients returning to IKDC levels 1 and 2 activities.¹⁵

Limitations of soft tissue fixation and graft creep within the bone tunnels are probably responsible for the slightly inferior results compared with BPB grafts; however, the post-operative recovery and lower donor site morbidity have made this technique widely popular. Quadriceps tendon grafts have gained popularity because there is no associated anterior knee pain, a bone-plug is possible on one end of the graft, and they have appropriate biomechanical properties. Biomechanically, the ultimate tensile load has been reported as 1075–2353 N.^{3,20} Surgically, it is critical to avoid damage to the articular cartilage because the articular surface extends to the edge of the tendon.³ Bone to bone fixation can be achieved on one end; soft tissue fixation and its associated limitations must be utilized on the other end of the graft. Limited data are available on the results of ACL reconstruction with quadriceps tendon. It is most commonly used in revision ACL reconstruction or in knees with multiple ligament injuries.³ Donor site morbidity includes quadriceps muscle atrophy, articular surface damage at harvesting, scar size, and location.³ At the start of the twenty-first century, orthopedic surgeons use autogenous tissue to restore knee stability to a high percentage of patients and return the majority to their previous level of athletic activity. Each of the grafts has shortcomings that an alternative, biologically relevant graft source could overcome.

4. Allografts

Allografts are becoming more widely used with improvements in methods of procurement, sterilization, and storage. Graft options include bone-patellar tendon-bone, hamstring, tibialis, Achilles' tendon, and fascia lata.²¹ These grafts are obtained from organ donors ranging in age from 15 to 45 years old. Early methods of allograft processing resulted in significant weakening of the tissue and potentially toxic by-products. New, improved methods of procurement, sterilization and storage only minimally weaken the grafts.³ Utilization of an allograft decreases operative time and eliminates donor site morbidity associated with autologous tendon harvest; however, surgeons still face challenges with fixation. Recent reports indicated that allografts revascularize to become biologically viable in a similar fashion as autografts,¹² indicating the potential for long term function. Overall stability is nearly comparable to autogenous grafts in long term (>5 years) studies.¹² The post-operative recovery is faster and less painful with allografts because of the shorter surgical time and elimination of donor site morbidity. The risk of infection and disease transmission is low, but according to some physicians and many patients remains the major limitation in the use of allografts. The death of a patient in 2001 in Minnesota who had an allogenic meniscal transplantation has reinforced this perception. The lack of appropriate organ donors remains a problem in the widespread use of allografts.

5. Synthetics

In the late 1970s and early 1980s the orthopedic community trialed ACL substitutes with the goal of high initial strength and rigid fixation, immediate mobilization, and a faster return to sports. A recent review reported that 40–78% of 855 prosthetic ligaments (tracked for 15 years) failed over time.²² The grafts failed secondary to wear debris, tissue reactions, and mechanical limitations of the grafts. The first generation of ACL prostheses included polytetrafluorethylene (Gore-Tex[®]), polyester (Dacron[®]), carbon fiber, and polypropylene ligament augmentation devices (LAD). Evaluating the method of failure of these prostheses has provided the basis for renewed research. Synthetic devices can be categorized as true prostheses, scaffolds, and augmentation devices. True, or permanent, prostheses are designed to have high strength and increased resistance to fatigue failure. Their

mechanical properties are primarily responsible for withstanding forces over a long time period without support from tissue ingrowth or autogenous tissue. Scaffolds allow for autogenous tissue ingrowth. The new collagen tissue should eventually grow to replace the ligament. Augmentation devices, or stents, are temporary prosthetic ligaments designed primarily to increase the immediate strength of the graft and augment the security of fixation of the tissue.^{23,24}

Mechanical properties of various ACL implants:

Prostheses	Ultimate tensile strength	Elongation	Stiffness
Gore-Tex [®]	5300 N	9%	322 N/mm
Dacron [®]	3631 N	18.7%	420 N/mm
Carbon fiber	660 N	1%	230 × 10 ⁹ N/mm

Advantages and disadvantages of various ACL implants:

Prostheses	Advantages	Disadvantages
Gore-Tex [®]	High strength and fatigue life; limited particulate debris	Lack of tissue in-growth; fraying at bone tunnels; chronic effusions; ultimate longevity
Dacron [®]	High strength, supported collagenous in-growth	Stress-shielding of collagenous in-growth; rupture of the femoral or tibial insertion; rupture of the central body; elongation
Carbon fiber	Synthetic material	Particulate matter; foreign body response in synovium
LAD*	Protects graft during maturation	Inflammatory reaction; high complication rate

*LAD, ligament augmentation device.

The strand is woven into a three-bundle multifilament with fixation eyelets at each end of the ligament. The prosthesis has been implanted in more than 18,000 patients worldwide.²³ This prosthesis was expected to function effectively as a replacement because it was not dependent upon in growth of tissue to increase its strength over time. It was designed to give immediate fixation with early load-bearing capabilities, thus promising early mobilization and return to activity.²⁵ The ultimate tensile strength of the prostheses is approximately 5300 N with a stiffness of 322 N/nun. The ultimate strain of the material is 9%.²³ The Gore-Tex[®] graft ultimately failed from material fatigue because of the lack of tissue in growth, fraying at bone tunnels, and chronic effusions.²³ Despite excellent biomechanical properties, the graft was unable to withstand the cyclic loads of active individuals. The ligament was approved by the FDA for use only in previously failed autogenous reconstructions. To address these issues, a Gore-Tex II[®] prosthesis is currently being tested in Canada. This new version has been designed with a compact diameter consisting of a tighter weave to prevent abrasion of the ligament, increase the longevity of the implant, and reduce particulate shedding.²³ The Dacron ligament was designed as a scaffold, prostheses hybrid to solve the problems of stiffness that led to high failure rates in previous devices. The strength of this device was thought to be sufficient to withstand stress and resist fatigue.²⁶ The Dacron[®] prosthesis consists of a core of four, tightly-woven Dacron[®] tapes that are encased by a sleeve of loosely-woven Dacron[®] velour, which promotes abundant tissue ingrowth. The prosthesis is 8 mm with a

mean ultimate tensile strength of 3631 N and a mean ultimate elongation of 18.7%. Fatigue is reached at 134,000 cycles at 1730 N.²³ Complications resulting from the Dacron[®] prosthesis included rupture of the femoral or tibial insertion of the ligament, rupture of the central body of the prosthesis, and elongation of the ligament. The decline in the ligament strength with time may be caused by the permeation of synovial fluid and connective tissue.²⁷ Significant tissue in-growth was noted, but secondary to stress shielding from the core of Dacron[®] tapes, the tissue was not functional in knee stability. Rupture of the ligament at the bony insertions was probably caused by the fraying of the Dacron[®] by the sharp edges of the tunnels.

The carbon fiber device was designed as a scaffold that would support the rapid ingrowth of fibroblastic tissue and thus, produce new collagen.²³ The carbon fiber prosthesis is formed from 40,000 carbon fibers (Plastafil[®]) in two or three parallel, twisted bundles coated with biodegradable medical grade gelatin. The individual fibers are 8–10 [mm in diameter]. The ultimate tensile strength of the twisted bundles is approximately 660–1600 N (depending on weave), with a stiffness of 230×10^9 N/mm, and elongation at failure was 1%.^{28,29} The predominant complication associated with carbon fibers was particulate matter. Free carbon fibers were found within the joint and migrated from the knee to regional lymph nodes.³⁰ The Kennedy Ligament Augmentation Device⁶ was designed to provide protection to a primary repair of the ACL or autologous quadriceps patellar tendon over-the-top reconstruction. The graft was designed to protect the repair or graft while it healed to avoid the risk of rupture. This LAD is composed of a ribbon of polypropylene woven from eight braids. The LAD is 8 mm in diameter and has an ultimate tensile strength of 1730 N and a stiffness of 56 N/mm. Ultimate elongation at failure is 22%.²³ The LAD is predominately of historic interest because primary repair of the ACL is not routinely performed and the over-the-top reconstruction has been supplanted by newer techniques. A recent review of the LAD concluded that because of complication rates of up to 63%, a delay in the maturation of the biological grafts via stress shielding, and excellent results without augmentation LADs are not advocated in primary ACL reconstruction.³² New approaches entering the twenty-first century, ACL reconstruction can be predictably performed using autogenous and allogenic issue grafts. The significant limitations associated with each tissue graft have stimulated a re-evaluation of treatment methods. Previous attempts at primary repair and synthetic replacement of the ACL were less than successful. With a better understanding of the ACL and joint biology, the cellular and genetic blueprint of the ACL, and the ligament's response to injury, new research has been directed toward the development of biologically and mechanically relevant tissue to treat ACL ruptures.

6. Potential for ACL repair

The first reported primary repair of the ACL was performed by Mayo Robson in 1885 in England.³³ Subsequent authors have reported high rates of failure; primary ACL repair is not a mainstream treatment for ACL ruptures.²¹ It is hypothesized that the repaired ACL fails to heal because of a combination of factors including lack of formation of a blood clot, lack of vascular supply, deficits in intrinsic cell migration, impaired growth factor availability, and environmental effects of the synovial fluid on cell morphology.^{22–34} These problems have led to research into the biology of the ACL's response to injury and healing. Lo et al.³⁵ reported that ACL fibroblasts from torn ligaments had the ability to up-regulate ligament specific markers including collagen types I and III and tissue inhibitor metalloproteinase-1 (an inhibitor to collagenase) for up to 1 year post-trauma. These findings are indicative of the ACL's potential ability to heal post-trauma. In vitro

studies have shown that ACL fibroblasts can migrate across scaffolds and potentially heal a defect, but not if the gaps are larger than 50 μ m.^{34,36,37} Investigations into the healing of extra-articular ligaments such as the medial collateral ligament have shown that a blood clot functions as the scaffold that allows fibroblasts to migrate and heal the defect.^{34,36} Intra-articularly, it has been shown that no blood clot forms to provide a scaffold for repair of a ruptured ACL.³⁸ Even with macroscopic re-approximation of the ligament, the lack of a blood clot scaffold inhibits the ability of the ACL to heal itself. Implantation of an engineered scaffold which could hold the ligament ends in microscopic proximity, resist synovial degradation, and stimulate cell invasion and regeneration could provide success for primary repair of the ACL.³⁴ Research into scaffolds and optimization of the intra-articular environment within growth factors or gene delivery are actively being pursued.³⁷

7. Bioengineered ACL

The lessons learned from the side effects of autologous and allogenic grafts, and the first generation of prosthetic grafts must be considered if attempts to engineer a viable and fully functional ACL replacement are to be realized. The following key criteria should be incorporated into the design of the prosthetic device if it is to be successful over the long term. The prosthesis should:

- Cause minimal patient morbidity.
- Be surgically simple to insert and have reliable methods of fixation which will withstand aggressive rehabilitation.
- Produce and maintain immediate stabilization of the knee without tissue-fixation device creep to allow patients to rapidly return to their preinjury level of function.
- Present no risk to the patient for infection or disease transmission.
- Be biocompatible and not elicit a host immune response.
- Support host tissue ingrowth.
- Direct host tissue ingrowth without causing stress-shielding, i.e., the prosthesis must adequately communicate environmental signals (both mechanical and biochemical) to the developing host tissue so ingrowth is properly directed and organized.
- Biodegrade, i.e., be capable of being metabolized by the host at a rate that provides adequate mechanical stability during replacement by new extra-cellular matrix (ECM).
- Maintain mechanical integrity prior to degrading, either in vitro or in vivo, for a duration sufficient to allow host tissue ingrowth and organization to eventually maintain the mechanical integrity of the ACL over the lifetime of the patient.

Ideal histological outcomes would include the graft developing structure identical to the native ACL (including the collagen crimp pattern) within 3–6 months in vivo. Biomechanically, the graft must possess the mechanical characteristics (mirror the ACL's stress-strain curve) of the native ACL at the time of surgery, post-operatively and for decades into the future. To succeed, the goal must be a tissue engineered ACL that enables the development of functional and biologically relevant ACL host tissue to ensure the continual cascade of ligament remodeling and degradation over the lifetime of the patient. Tissue engineering can potentially provide improved clinical options in orthopedic medicine through the generation of biologically based functional tissues for transplantation. A tissue engineered ACL with the appropriate biological and mechanical properties would eliminate many of the deleterious effects associated with autologous and allogenic grafts, including donor site morbidity and the risk of disease transmission. A graft that provided immediate strength and maintained it post-

operatively, could eliminate the need for its protection (approximately 6 months for biologic tissue) and return athletes to sports more rapidly. In the early 1990s, Dunn et al.³⁹ reported on the development of a second generation ligament prosthesis combining the advantages of synthetic materials (high strength, simple fabrication, and storage) and biologic materials (biocompatibility and ingrowth). Initial work involved a collagenous ACL prosthesis composed of reconstituted type I collagen fibers in a collagen I matrix with polymethylmethacrylate bone fixation.³⁹ Results showed inconsistent neoligament formation and significant weakening of the prosthesis in a rabbit model. Enhanced scaffolds were examined including a collagen fiber-poly-lactic acid (PLA) composite to further maintain mechanical integrity and allow for neoligament tissue ingrowth.⁴⁰ In both studies, only half of the structures remained intact 4 weeks post-reconstruction. Dunn et al.⁴¹ and Bellincampi et al.⁴² hypothesized that neoligament formation could be improved by pre-seeding a scaffold with autogenous ACL and patellar tendon fibroblasts.

8. Conclusion

The future of treatment of the ACL rupture is changing as our understanding of the biology surrounding the ACL continues to increase. It is our expectation that clinically applicable treatments, including the repair of the ACL and the development of a biologically engineered ACL, will occur in the next decade.

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Further reading

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