Structure and Function Are Not the Same: The Case for Restoring Mechanoreceptor Continuity Following Anterior Cruciate Ligament Injury

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ABSTRACT

Anterior cruciate ligament (ACL) injury, particularly in increasingly young and active adolescents, continues to pose a clinical challenge with re-injury rates reported as high as 30%. Evidence also suggests that current standard-of-care ACL reconstruction (ACLR) does not mitigate post-traumatic osteoarthritis (PTOA) risk. Bridge-enhanced ACL restoration (BEAR) is a recently developed and tested ACL surgery that promotes primary healing of the native ACL with excellent early results. BEAR has shown to reduce signs of early PTOA compared to ACLR in an animal model. Here, we describe a theoretical framework related to re-innervation that can clarify why the outcomes of ACLR and BEAR surgeries differ. We also discuss how ongoing and new challenges in determining return-to-sport readiness following the competing surgeries may differ, and how emerging imaging tools and measures of neuromuscular function may aid in clinical decision-making to decrease the likelihood of re-injury and PTOA risk.

KEYWORDS: ACL, neuromuscular, kinematics, surgery, post-traumatic osteoarthritis

THE ONGOING CLINICAL CHALLENGE OF TREATING ACL INJURY

The anterior cruciate ligament (ACL) is one of the most frequently injured knee ligaments with up to 400,000 ACL tears occurring in the US annually.[1,2] Of these occurrences, teenagers are the most at-risk population.[3,4] This adolescent demographic presents a particularly challenging clinical problem as ACL tear increases the risk of post-traumatic osteoarthritis (PTOA), with up to 50–80% of these young patients developing symptomatic OA within 10 to 20 years of their injury.[5-7] Given there are no known disease-modifying therapies for PTOA, the injury leaves these typically young adults to manage their condition over most of their lifespan. Further, ACL re-injury is not uncommon and has been reported to be as high as nearly 30% in athletes under the age of 20[8] with subsequent inferior patient outcomes after graft failure.[9] These observations underscore the need to identify mechanisms that modulate re-injury and PTOA risk following ACL tear and to augment current treatment strategies to improve patient outcomes.

## PRIMARY REPAIR AS AN EMERGING TREATMENT FOR ACL INJURY

Spontaneous healing of the ACL is rare and if left untreated, the knee is unstable with many patients unable to perform activities of daily living, let alone resume sports. ACL reconstruction (ACLR) is the current standard of care and involves drilling bone tunnels through the footprints of the ACL and replacing the torn ligament with a tissue graft harvested from elsewhere in the body. ACLR grossly restores knee stability and allows many patients to resume pre-injury activities, but the procedure does not mitigate PTOA risk[10] or fully restore clinical, functional, and patient-reported outcomes (PROs).[11-13] Reasons for these shortcomings remain elusive with measures of knee laxity, patient demographics, societal factors, surgical treatment and the need for subsequent revision surgery explaining only 10–20% of the variation in PROs in a multivariable regression analysis of nearly 1600 ACLR patients followed prospectively for 10 years (NCT00478894).[9] Thus, factors not yet fully captured by these clinical trials may be important modulators of long-term patient outcomes and joint health. Bridge-enhanced ACL restoration (BEAR), is a surgery that involves use of an FDA-cleared extracellular matrix sponge to create a stable blood clot that allows the torn ACL ends to reconnect through primary wound healing[14] (**Figure 1 A,B,C**).

BEAR has several advantages over conventional ACLR, including the elimination of graft donor site morbidity associated with autograft procedures (e.g., patellar tendon, hamstring, and quadriceps tendon),[16] and as we speculate here, the potential to preserve ACL mechanoreceptor machinery. Alongside restoration of the double bundle morphology of the native ACL, these distinguishing features may explain the more rapid and complete recovery of knee extensor and flexor strength and functional hop test performance following BEAR compared to ACLR patients within the first two years after surgery.[17,18] These differential responses were noted despite the presence of similar magnitudes of residual joint laxity between the competing surgeries. We believe that this observation points to the presence of mechanisms other than graft biomechanical function that modulate early patient outcomes.

INNERVATION AND PTOA RISK

In developing the BEAR procedure, one of the exciting outcomes observed in the animals that underwent BEAR was

Figure 1. [A] Following ACL tear, [B] ACLR involves removing the ACL and replacing it with a tendon graft by drilling bone tunnels through the footprints of the ACL so that the graft can be introduced into the joint. [C] BEAR is an alternative approach that uses a suture bridge through small bone tunnels drilled adjacent to ACL footprints to provide initial stability while the extracellular matrix sponge soaked with autologous blood creates a stable blood clot that promotes primary wound healing. [FIGURE IS USED WITH PERMISSION FROM MURRAY AND FLEMING[15]]
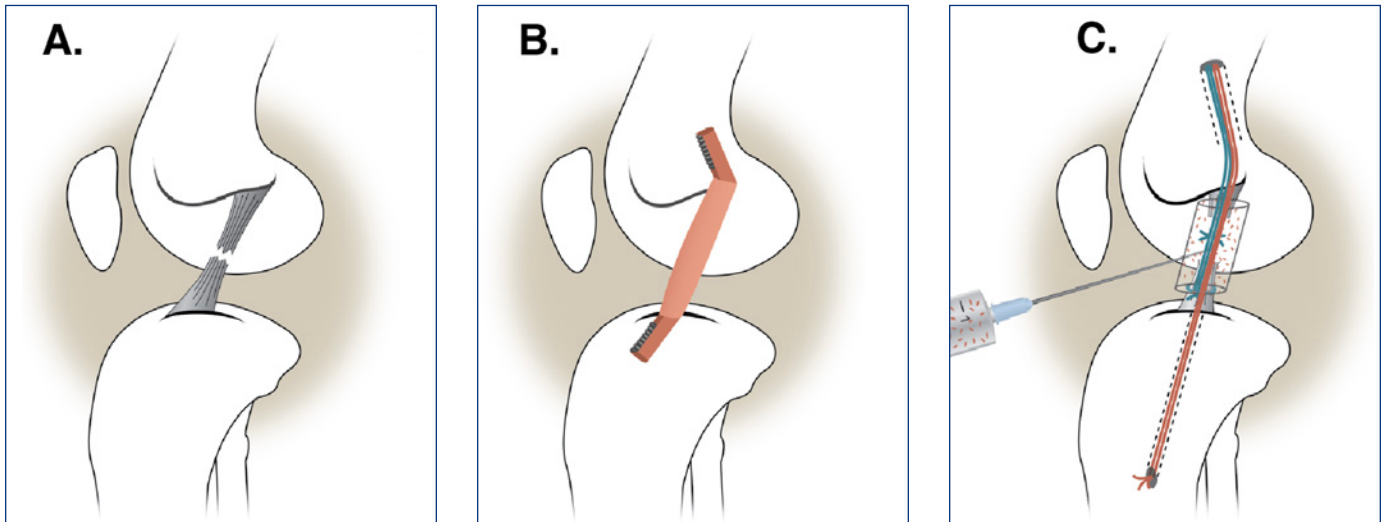
that they had less cartilage damage – a hallmark of PTOA – compared to animals that underwent ACLR.[15,19] Meanwhile, the biomechanical properties of the grafts and repaired ACLs were similar.[15,19] Several subsequent pre-clinical studies have failed to identify biological modulators that might explain the differential cartilage outcomes observed by 12 months in the animal models.[20-22] Interestingly, hind limb loading was similar between the competing surgeries up to six months after surgery, but it diverged between 6–12 months.[23] This leads us to hypothesize that the functional divergence might reflect a different neuromuscular strategy conferred by the preservation of the mechanoreceptor anatomy that would occur with BEAR, but may not be present following ACLR because of the bone tunnel drilling required for graft placement and removal of the injured ligament. Evidence from small animal models adds further support to this working hypothesis, whereby severe osteoarthritis develops when the mechanoreceptor signaling pathway in the knee is surgically ablated without disturbance to the intra-articular connective tissues.[24] With respect to the ACL specifically, the native ACL contains mechanoreceptors[25] with the majority located in the epiligament and bony insertions.[26,27] ACL mechanoreceptors – Ruffini corpuscles, Pacinian corpuscles, and Golgi-like tendon organs – relay afferent communication about joint position and ligament tension to the central nervous system,[28-30] whereas free nerve endings are believed to contribute primarily to nociception.[31] However, debate remains as to which tissues (e.g., synovium, capsule, menisci)[32] contribute to proprioceptive and nociceptive information.[31] Nevertheless, a reflex arc exists between the ACL and hamstring muscles, that when elicited by direct mechanical tensioning[33] or electrical stimulation of the ACL,[34] hamstring contraction is triggered. Because hamstrings are antagonists to anterior tibial translation[35] – the direction of motion constrained primarily by the ACL[36] – their activation under excessive ACL tension would off-load the ACL.[37] This protective reflex arc is either absent[38] or significantly diminished following ACLR.[34,39] Thus the inability of the central nervous system to accurately detect changes in ligament tension and respond would result in joint proprioception deficits. Conversely, if BEAR restores the neural connectivity between the two torn ends of the ACL, its sensory function may also be restored and would promote more normal neuromuscular and kinematic function.

PERSISTENT ABNORMAL NEUROMUSCULAR FUNCTION AND KNEE KINEMATICS

When faced with reduced afferent proprioceptive input and compromised spatial awareness of a limb due to ACL injury, individuals may experience challenges in actively constraining joint orientation through coordinated muscular contractions. This hypothesis builds on the longstanding observations that ACLR patients demonstrate residual abnormal knee kinematics after surgery.[40,41] Our recent work has shown that ACLR subjects land from a hop with their tibia positioned more anteriorly[42-44] and that their neuromuscular function remains different from that of controls' more than a decade after surgery.[45-47] Greater anterior tibial translation and more rapid sliding between contacting tibiofemoral surfaces have shown a direct and linear correlative relationship to the amount of cartilage damage observed in a large animal model of ACL transection.[48,49] Thus, if neuromuscular function does not adequately constrain this

motion, PTOA onset could result. What is known from the animal models in terms of damaging contact mechanics and their relationship to PTOA dovetails the variable rate of PTOA onset observed clinically, with some ACLR patients remaining asymptomatic for decades while others develop early degenerative changes.[5-7,9] ACLR and post-operative rehabilitation aim to target these structural and functional mechanisms thought to be mechanical drivers of PTOA risk, though they fail to do so in many patients.[10]

REHABILITATION AND RETURN-TO-SPORT (RTS) READINESS

Following either ACLR or BEAR surgery, the primary goal of rehabilitation is to diminish pain and swelling and to regain lower limb flexor and extensor muscle strength and function by implementing a progressive program that sequentially targets knee range of motion, lower limb strength, and dynamic plyometrics.[50,51] Despite following best practices and careful clinical oversight, evidence suggests that few patients pass all functional test criteria designed to inform RTS readiness.[52] Alarmingly, re-injury rates as high as 30% within the first five years of injury have been reported.[8] Of note, this statistic includes the risk of contralateral injury, which appears to be highest within the first year of index ACL injury.[8] There is mounting evidence that peripheral and cortical processing changes indicative of central nervous system reprogramming[41] also occur during this two-year post-injury time frame.[53,54] Why these systemic changes occur is speculative, but because nature favors symmetry[55] we posit that the central nervous system may undergo a degree of reorganization to re-establish lower limb symmetry. If the nervous system is undergoing a rapid state of flux by adapting both injured and contralateral limb function, it may heighten ACL injury risk already present because of underlying factors (e.g., posterior tibial slope, narrow notch width, ACL size, genetic susceptibility).[56,57] To this point, our data demonstrate that neuromuscular[47] and kinematic[44] function of the contralateral limb appear more similar to the ACL-injured limb of ACLR patients than those of healthy controls 10+ years after injury. The cross-sectional nature of that work precludes us from ascertaining whether these neuromuscular and kinematic differences were inherent to these patients and could reflect why they were injured to begin with; however, longitudinal studies by others suggest contralateral kinematics gradually change over time, dovetailing the movement patterns of the ACLR limb.[58,59] In a similar vein, PROs likewise change rapidly over the first two years after ACLR before plateauing.[9,11] Taken together, there appears to be a rapid period of local, systemic, and psychological adaptation before reaching a steady state at two years post-surgery.

SPECIAL CONSIDERATIONS FOR BEAR PATIENT REHABILITATION AND RTS READINESS

Preliminary clinical studies have demonstrated that BEAR patients are passing functional benchmarks earlier, have a more rapid and complete restoration of knee flexor and extensor strength, and report greater psychological readiness to RTS.[17,18] This accelerated recovery following BEAR poses a new set of challenges for the rehabilitation team, whereby the patient may feel ready to engage in more dynamic activity, but the healing ACL may not be sufficiently remodelled to withstand the magnitude of tensile loading it may undergo, as preclinical studies suggest the healing ACL continues to gain tensile strength and stiffness up to 12 months after repair.[19] Further, there are temporal differences between the biological remodelling of an implanted tendinous graft and primary healing of the native ACL. The ACL graft undergoes "ligamentization", during which it gets progressively weaker as it is revascularized before regaining ultimate tensile strength and stiffness as the collagen is remodelled; however, graft structural properties never fully recapitulate those of the native ACL with inferior graft stiffness and diminished tensile strength.[60] In the case of BEAR, the repair is weakest in the immediate postoperative period followed by a gradual increase in structural properties as the provisional synovial scaffold is remodelled into organized collagen.[61] Work in animal models suggests that the functional end point is ultimately the same between the competing surgeries,[15,19] but there is currently no consensus on how best to promote optimal functional healing following BEAR, neither tools or metrics capable of probing the structural properties of the ACL directly to monitor how they may respond to mechanical cues. There is thus an opportunity to address these clinical gaps with novel metrics that capture the underlying biological healing processes and their relationship to neuromuscular function more directly.

EMERGING TOOLS TO GAUGE RTS READINESS

Clinical exams, functional tests, and PROs are staples of clinical and research toolboxes used to judge the integrity of the implanted ACL graft and a patient's overall physical and psychological readiness to RTS; however, they are poor predictors of re-injury risk.[52] Using magnetic resonance imaging (MRI) to predict when the tissue would be able to withstand tensile forces associated with sport participation would be a valuable tool. Our research group has made progress towards this end,[62-65] where we have shown its promise in predicting graft/ACL failure.[62,66] Nevertheless, the imaging approach does not capture the role that the neuromuscular system may play in graft/ACL remodelling or contralateral injury risk.

Using conventional motion capture (MoCap) to determine joint kinematics and kinetics has provided insight into the functional recovery following ACLR,[59] but has yet to identify the "smoking gun" between biomechanical abnormalities

and PTOA pathogenesis, possibly due to limitations associated with the accuracy[67] required to record dynamic movements that are most likely to be associated with greater re-injury risk, such as jump landings and cutting maneuvers.[67] Common to all kinematic measures is that they are largely the result of neuromuscular function; capturing how muscles are activated, the quality of their contraction, and their coordination may be a more direct measure of neuromuscular changes and their potential differential response to ACLR versus BEAR, as well as contralateral injury risk.

The most common and least invasive way to acquire measures of muscular activation entails using surface electrodes placed over the muscle bellies of interest to record electromyography (EMG) signals. We have recently demonstrated that analysis of the frequency content of signals acquired from EMG provides rich information capable of distinguishing subtle differences in muscle activation patterns between ACLR patients and healthy control subjects.[46] Importantly, these differences were not detected in the same subjects using conventional EMG approaches that analyzed only the timing of muscle activation.[45] Another important finding was that our approach additionally identified contralateral limb differences in ACLR patients,[47] which could prove to be a useful metric for tracking systemic changes in neuromuscular function after ACL injury. With support from the Injury Control Center of Biomedical Research Excellence (COBRE) at Rhode Island Hospital, work is ongoing to determine the extent ACLR and BEAR neuromuscular activation patterns are different after two years of healing, and how they relate to knee kinematics and PROs. As the work matures and we learn more about the neuromuscular features that distinguish the two surgeries, we hope to develop a framework that uses lower limb EMG-based machine learning to identify rehabilitation milestones that would have utility in determining RTS criteria.

THE ROLE OF INFLAMMATION

It is worth noting that although we have focused on the structural and functional differences between ACLR and BEAR, it is possible that the molecular environment also plays an important role in the long-term risk of PTOA.[68] As we eluded to earlier, several subsequent studies in the porcine model of ACLR and BEAR investigated whether pro-inflammatory cytokine concentrations and RNA expression in the synovium, synovial fluid, and articular cartilage differed between the competing surgeries.[21,22,69-74] Two notable findings emerged: 1) there are no differences in the RNA transcriptome within the first four weeks post-op between the competing surgeries;[22,69] 2) inflammatory mediators and metabolic markers detectible in the synovial fluid are upregulated following only BEAR,[70] and only by 12 months are differences in synovial fluid proteome detectible[21] with a greater abundance of cytokines being chondroprotective.[72]

It is also worth reiterating that the temporal emergence of the differential molecular outcomes parallels the emergence of a different gait strategy,[23,72] which provides additional evidence that neuromuscular control may play an important chondroprotective role and may even influence the molecular environment. These are ongoing topics of investigation.

SUMMARY

Whereas ACLR continues to be a successful surgery insofar as it restores gross knee structure and stability following ACL tear, it may not restore the native ligament's neural connectivity and the more fine-tuned neuromuscular control necessary to fully recapitulate pre-injury function. BEAR is an emerging surgical approach that may preserve mechanoreceptor function and in-turn promote a more complete neuromuscular and kinematic recovery that mitigates PTOA risk. Emerging tools being developed in the research setting offer promise towards providing insight into the functional status of the healing ACL and the neuromuscular system with the goal of reducing re-injury risk and augmenting the clinician's ability to guide RTS decision-making following ACL surgery.

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