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Optimizing Outcomes of ACL Surgery – Is Autograft Reconstruction the Only Reasonable Option?

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Abstract

ACL injuries occur at a high frequency in the US with approximately 400,000 ACL reconstructions being performed each year[1]. While ACL reconstruction is our current gold standard of treatment, it does not restore joint motion[2–4], or prevent the premature development of post-traumatic osteoarthritis (PTOA) in many patients[5–9]. Thus, new treatments for an ACL injury, which are less invasive and minimize patient morbidity, including cartilage damage, are highly desirable[10,11]. We have used a tissue engineered approach to stimulate ligament healing, to improve upon current treatment options[12]. In this review, we describe and discuss our work moving a tissue engineering strategy from the concept to bench, preclinical, clinical trials and ultimately FDA 510(k) de Novo approval, providing clinicians and patients with a viable alternative to ACL reconstruction.

Keywords

Anterior cruciate ligament; tissue engineering; ACL reconstruction; ACL repair; bridge-enhanced ACL repair; scaffold-enhanced ACL repair; post-traumatic osteoarthritis; platelet; clinical trial

Background

The clinical problem

Unlike other ligaments, like the medial collateral ligament of the knee, the anterior cruciate ligament (ACL) fails to heal after injury[13]. In addition, using sutures to repair the ACL has a high failure rate[14], even with modern techniques[15]. When the high failure rate was noted in the 1970s, surgeons began adding a reinforcing strip of tendon or fascia to the repaired ACL to protect it[16], and eventually moved to only using a graft – typically a strip of bone/patellar tendon/bone and then using two of the hamstring tendons (semitendinosus and gracilis)[17,18] or part of the quadriceps[19] tendon harvested from the patient. The downside of taking a graft from the patient also led to a rise in the use of allograft tendons; however, the significantly higher failure rate in active patients[20] led to a dampening of the use of allograft tendons in athletes[21].

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The current gold standard of care, ACL reconstruction (ACLR), is performed by drilling tunnels, typically 8 mm to 10 mm in diameter, in the femur and tibia, harvesting the graft from elsewhere in the knee (extensor mechanism or hamstring tendons), passing the graft through the tunnels and securing it to the bone with screws or another fastening mechanism. This operation results in good stability of the knee and approximately 65% of patients can get back to their preinjury sport level[22]. Patients do, however, continue to experience weakness in the area where the graft was taken[23], and the graft retear rate in teenagers is 15-20%[24–26]. In addition, patients who tear their ACLs have an increased risk of developing osteoarthritis of the knee – an estimated 74% will develop this on radiographs in only 14 years after the initial injury[6]. This is a large burden for patients who tear their ACL in their teen years.

Addressing the Clinical Problem

In thinking about this clinical problem and the current gold standard of treatment, a treatment for ACL injuries that would not require graft harvest or replacement of the torn ligament with a tendon was of interest. The ACL is one of few tissues in the body that is treated by removal and replacement, rather than with surgical repair. To determine if healing would be possible, our initial investigations focused on the biologic response of the ACL – defining the key functions required for wound healing and determining which are impaired for this ligament. Identification of the defect in wound healing biology would then enable design of a strategy to address the defect.

The Pathologic Analysis

Systematic pathologic examination of the torn ACL tissue[13] and the response of the ACL cells in the torn tissue to injury, and then comparative animal models evaluating the response in the medial collateral ligament (MCL) and ACL, revealed that ACL cells and vessels were capable of proliferation, migration and collagen production after injury, much as MCL cells were[13,27–31]. While the MCL had the surgically created defect fill in with blood that solidified into a scaffold that could be remodeled into healing tissue, the ACL defect was filled with synovial fluid that remained liquid, and no bond between the torn ends was established[32,33]. With that constellation of pathologic findings, identification of a material that could be placed between the torn ligament ends to allow a protected space for healing of the ACL to occur drove the next phase of our investigation.

Preclinical Studies

After a series of in vitro studies of various materials and growth factor combinations, a hydrophilic scaffold made of collagen and other extracellular matrix proteins, which was able to soak up autologous whole blood from the patient and hold that blood in place between the torn ends of the ACL, was selected. This scaffold was combined with a suture repair of the ligament. Our studies in canine[32,33] and porcine[34–38] models demonstrated that the combination of the scaffold and suture repair (“scaffold-enhanced repair”) enabled the release of growth factors with spatial and temporal sequences that matched their release in healing extra-articular tissues, such as the MCL[32]. Focusing on the porcine model as a fit-for-purpose model for ACL injury [39,40] led to the finding that repair with the scaffold and blood resulted in a healing ligament that was more robust (Figure 1) and biomechanically

superior to repair with sutures alone[37], and had biomechanical properties similar to that of an ACL graft at time points up to one year after surgery (Figure 2). [34,41]

We also found that skeletally immature animals had a healing ACL with a 50% higher maximum load and stiffness at 15 weeks after scaffold enhanced repair[42,43] than adult animals, and that male and female animals had healing ACLs with different biomechanical properties when absorbable sutures were used, but not when nonabsorbable sutures were employed for the scaffold enhanced repair[44]. Lastly, we found that the animals treated with scaffold enhanced repair did not develop as much osteoarthritis as those treated with a tendon graft[34] (Figure 3). We have since repeated that study in a second group of animals and found the same result[45].

Clinical Studies

Safety Study (cohort study)

With reasonable results in the preclinical "fit-for-purpose" model, additional studies were completed to obtain Institutional Review Board (IRB) and US Food and Drug Administration approvals for a first-in-human study, the Bridge-Enhanced® ACL Repair (BEAR) Trial (NCT02292004)[46–48]. This first study was primarily designed to assess patient safety and had two 10 patient cohorts followed in parallel and prospectively recruited. Patients with a complete, midsubstance ACL tear were enrolled into two groups, one group had scaffold enhanced suture repair and one group had autograft hamstring reconstruction. All patients were over 18, and the average Marx activity score at the time of injury was 14 (out of a maximum score of 16), which correlates with performing cutting and pivoting sports a few times a week during the prior year. Patients selected the procedure they wished to have, and the post-operative examiners were blinded as to procedure and side of surgery during the follow-up examinations. The early results of that study at three months demonstrated that there were no joint infections or signs of significant inflammation in either group. There were no differences between groups in effusion or pain, and no failures by Lachman examination criteria. Magnetic resonance images from the scaffold enhanced repair and ACL-reconstruction knees all demonstrated a continuous ACL or intact graft (Figures 4 and 5).

In addition, hamstring strength at 3 months was significantly better in the scaffold enhanced repair group than in the hamstring autograft group (mean ± SD: 77.9% ± 14.6% vs 55.9% ± 7.8% of the contralateral side; $P < .001$).[50] We continued to follow these patients out to two years, and found that there were no graft or repair failures in either group. The IKDC subjective scores in both groups improved significantly from baseline ($P < .0001$) at 12 and 24 months, to 84.6 ± 17.2 in the ACL reconstruction group and to 91.7 ± 11.7 in the scaffold enhanced repair group. Arthrometer testing demonstrated mean side-to-side differences in AP laxity that were similar in the 2 groups at 24 months (scaffold enhanced repair, 1.94 ± 2.08 mm; ACL reconstruction, 3.14 ± 2.66 mm). Functional hop testing results were similar in the 2 groups at 12 and 24 months after surgery. Hamstring strength indices were significantly higher in the scaffold enhanced repair group compared with the ACL reconstruction group ($P = .0001$). In this small, first-in-human study, scaffold enhanced

ACL repair produced equivalent or better outcomes to ACL reconstruction with a hamstring autograft[49].

Randomized Control Trial of Scaffold Enhanced Repair vs ACL reconstruction with Autograft Tendon

The results of the first-in-human study led to IRB and US Food and Drug Administration approval for a second trial of this technique – a larger randomized controlled trial (NCT02664545; BEAR II Trial), where the examiners, patients, and physical therapists were blinded to the surgical procedure patient until after completion of the two year visit.[51] One hundred young and active patients (median age, 17 years; median Marx activity score at the time of injury, 16, the highest score on the scale) who had sustained a complete midsubstance ACL tear were randomly assigned to receive either scaffold enhanced ACL repair (n = 65) or autograft ACLR (n = 35). All patients had surgical treatment within 45 days of injury. In this study, 96% of the patients returned for 2-year follow-up and another 3 were contacted by phone at two years to establish the incidence of additional surgery on the surgical or contralateral knee in 99% of the patients. The patients who had scaffold enhanced ACL repair had similar IKDC score and instrumented AP laxity when compared to the patients who had an ACL reconstruction (Figure 6). In addition, the patients who had a scaffold enhanced repair had a significantly higher mean hamstring muscle strength index than the ACL reconstructed group at 2 years. In addition, 14% of the scaffold enhanced repair group and 6% of the ACLR group had a re-injury that required a second ipsilateral ACL surgical procedure, a difference that was not statistically significant (P = .32). Additional studies with larger numbers of patients are needed to determine if this is a true difference. Interestingly, the 8 patients who converted from scaffold enhanced repair to ACLR in the study period and returned for the 2-year postoperative visit had similar primary outcomes to patients who had a single ipsilateral ACL procedure, which bodes well for those who undergo ACLR after scaffold enhanced repair.[51]

To put these results in perspective relative to prior, larger studies of ACL reconstruction, the mean 2 year IKDC Subjective score was 85 points in the ACL reconstruction group in this trial, which is consistent with the 2 year post-ACL reconstruction scores reported by the Multicenter Orthopedic Outcomes Network (MOON) group (81 points)[54] and others (86 points).[55] The scaffold enhanced ACL repair patients had mean scores at 2 years (89 points) more similar to that previously reported for an uninjured age-matched cohort (89 points for men and 86 points for women).[56] The clinically important difference in IKDC score is thought to be over 11 points, so the differences between the scaffold enhanced repair results in this early trial and the established IKDC scores in larger cohorts (a difference of 8 points) may not be clinically significant. Similarly, prior studies of ACL reconstruction have reported mean side-to-side differences in AP knee laxity after ACL reconstruction ranging from (1.1 to 2.5mm) two years post-operatively,[57,58] similar to those seen in both groups of the randomized control trial.

Elevated re-injury rates in active adolescents are a well-acknowledged problem after ACL reconstruction[59,60], with revision rates for ACL reconstruction reported to range from 10% to 28%.[20,61–65] For adolescents undergoing simple repair (no augmentation with a scaffold),

the risk for reinjury, even in carefully selected patients and using modern techniques, is 49% at 2 years.[66] Thus, the revision rate of 14% seen in the scaffold enhanced repair group in the randomized control trial is 35% lower than the rate reported ed for suture repair without a scaffold in this patient population,[66] and is similar to that previously reported for autograft ACLR for this age group. Lowering the risk of reinjury after ACL surgery is an important topic, particularly as revision ACL surgery is known to result in lower patient reported outcomes[67]. Advances in rehabilitation strategies and return-to-sport evaluations, potentially including imaging prior to return[68–72], are likely to play a role in this, in addition to improvements in surgical techniques, patient selection and patient education.

In an effort to identify a non-invasive measure to predict healing ligament strength, imaging was performed in both the preclinical and clinical studies of scaffold enhanced repair. In those studies, magnetic resonance imaging (MRI) was useful in measuring the healing ligament volume and the quality of the tissue when specific sequences were utilized[69,73]. Both cross sectional area of the healing ligament and the tissue quality as measured by signal intensity correlate with the maximum load and stiffness of the healing ligament in preclinical models[70,73] and have been used to evaluate the healing ACL in the clinical trials[71,72]. In human patients, a larger cross-sectional area of the repaired ligament at six months was associated with having a notchplasty performed during the surgical procedure, as well as older age and male sex[72]. A lower signal intensity (indicative of tissue closer to normal ligament) was found for patients with a smaller posterior tibial slope and less strength recovery in the quadriceps muscle on the surgical leg at three months after surgery (possibly an indicator of less aggressive strengthening of that leg or greater protection in the first few months after scaffold enhanced repair). While some factors are not modifiable (sex, age), others may be surgically modifiable (tibial slope, notch size) and some may be addressed by altering the post-operative rehabilitation protocol (quadriceps strength deficit).

The use of platelet-containing autologous products, including platelet-rich plasma and whole blood, for musculoskeletal tissue repair has become more popular in recent years. [74–78]. In our preclinical work, we found that increasing the concentration of platelets did not enhance either scaffold enhanced ACL repair or ACL reconstruction enhanced with a sleeve scaffold containing platelets [79,80]. Mesenchymal stem cells, either obtained from peripheral blood, fat or bone marrow, were also not found to improve ACL repair in preclinical models[81]. In the scaffold enhanced repair randomized control trial, while platelets were not concentrated prior to delivery, the complete blood count of the blood added to the implant was recorded. The number of platelets delivered to different patients in that trial ranged from 144 to 336 K cells/ul (a two-fold difference between the lowest and highest values) and the range of white blood cell concentrations ranged from 3.9 to 19.2 K cells/ul (a five-fold difference between the lowest and highest values). The six-month MR images were analyzed for cross sectional area and signal intensity as noted above, and associations between those findings (as a surrogate for the healing strength of the ligament) were sought. The results were stratified by sex, and univariate and multivariate regression analyses determined significant correlations between blood cell concentrations on these 2 magnetic resonance imaging parameters. Adjusted multivariable analyses indicated that total platelet concentration and total white blood cell concentration had no significant effect on either magnetic resonance imaging parameter. This led us to conclude that for this range of physiologic platelet

and white blood cell concentration, any significant effect on cross-sectional area or signal intensity of the healing ACL at 6 months after scaffold enhanced ACL repair could not be detected. Given these findings, factors other than the physiologic platelet concentration and total WBC concentration may be more important in the rate and amount of ACL healing after scaffold enhanced ACL repair[82]. These factors may include the time from injury to surgery, the rehabilitation program after surgery, intrinsic healing ability of the individual or the neurovascular status of the ACL remnants at the time of scaffold enhanced repair.

In addition to the primary outcomes, imaging and blood cell work, we also studied the effect of sex on overall outcomes after scaffold enhanced suture repair. That analysis found no significant effect of sex on the either the IKDC or KOOS scores at time points up to two years after surgery[83]. There was also no significant effect of sex on instrumented AP laxity testing at 2 years, nor on rates of secondary ACL injury rates. Six months after surgery, however, males had a seven times larger deficit in hamstring strength on the operated leg and a five times larger deficit in quadriceps strength on the operated leg ($p<0.03$ for both comparisons), while females had significantly better single leg hop testing 6 and 12 months after surgery ($p<0.01$ for both comparisons). There were no differences in either measure by the two-year time point, suggesting the males had caught up in the ensuing months. Our findings are in contrast to previous literature evaluating the effect of sex after ACL reconstruction where women have been reported to have greater AP laxity of the knee[8485] and larger deficits in both quadriceps and/or hamstring strength after surgery. [86,87]

Conclusions

Scaffold enhanced ACL repair, where a suture repair is supplemented with a scaffold that can hold a patient's blood between the torn ends of the ACL and provide a protected space for healing, has moved from bench to clinical trials. The initial results of the first two trials, including Level 1 evidence of similar performance of scaffold enhanced repair to the current gold standard of ACL reconstruction with autograft, are promising and have resulted in FDA Marketing Approval of the first implant labeled for use in augmenting ACL healing. The preclinical model and clinical study results justify continuing on this new avenue for research into improving outcomes of patients with ACL injuries. Future studies to optimize the surgical technique and rehabilitation strategies are likely to further improve outcomes, with scaffold enhanced ACL repair providing a less invasive, equally effective, option for treatment of mid-substance ACL tears.

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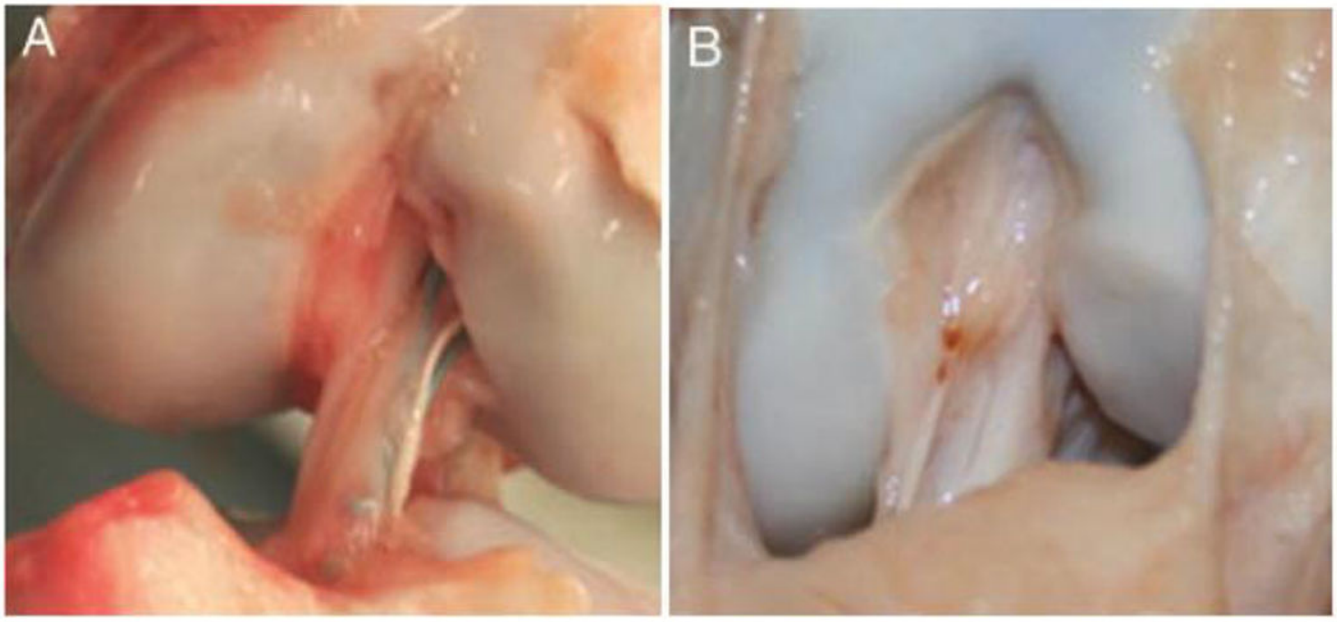

Figure 1:
Scar mass as seen at three months after (A) simple suture repair and (B) scaffold enhanced suture repair where a protein scaffold carrying blood components was placed between the torn ligament ends at the time of repair. Ligaments treated with the scaffold enhancement had a larger and more organized scar mass at three months, with a gross appearance closer to that of an intact porcine ACL. (Figure from Joshi et al, AJSM 2009[37]).

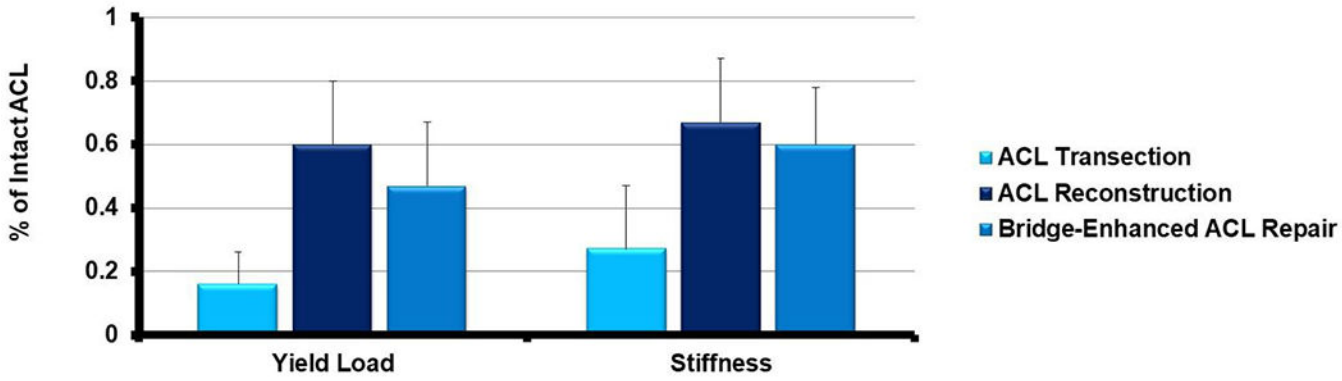

Figure 2:

The yield load and stiffness of the ACL at one year after ACL transection (light blue bar), ACL reconstruction (dark blue bar) and repair enhanced with a scaffold (medium blue, "bridge-enhanced ACL repair") at one year after surgery. There was no significant difference in mechanical properties between the ACL reconstruction group and the scaffold enhanced repair group[34]. Both reconstruction and scaffold enhanced repair had significantly improved mechanical properties when compared to ACL transection[34].

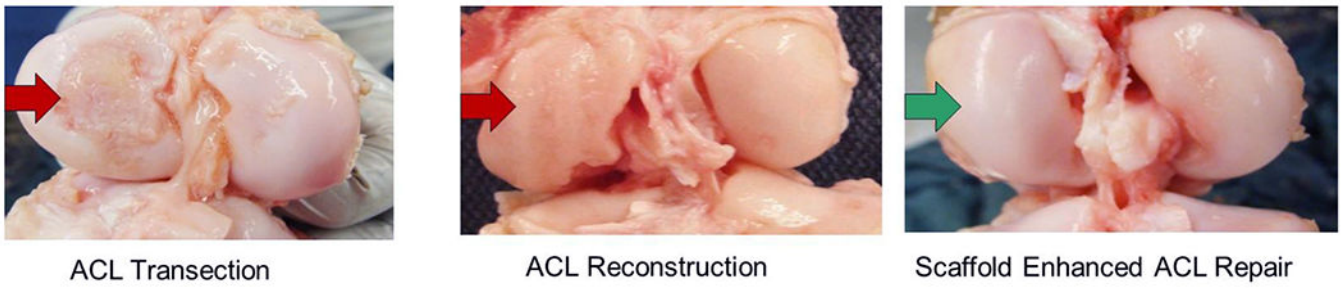

Figure 3:

Porcine knees at one year after ACL transection with no further treatment (left panel), ACL reconstruction (center panel) and scaffold-enhanced ACL repair (right panel). In the ACL transection and ACL reconstruction knees, breakdown of the cartilage in the medial femoral condyle is noted (red arrows), while in the scaffold enhanced repair group, there was no significant loss of cartilage integrity (green arrow; adapted from Murray and Fleming, AJSM 2013[34]).

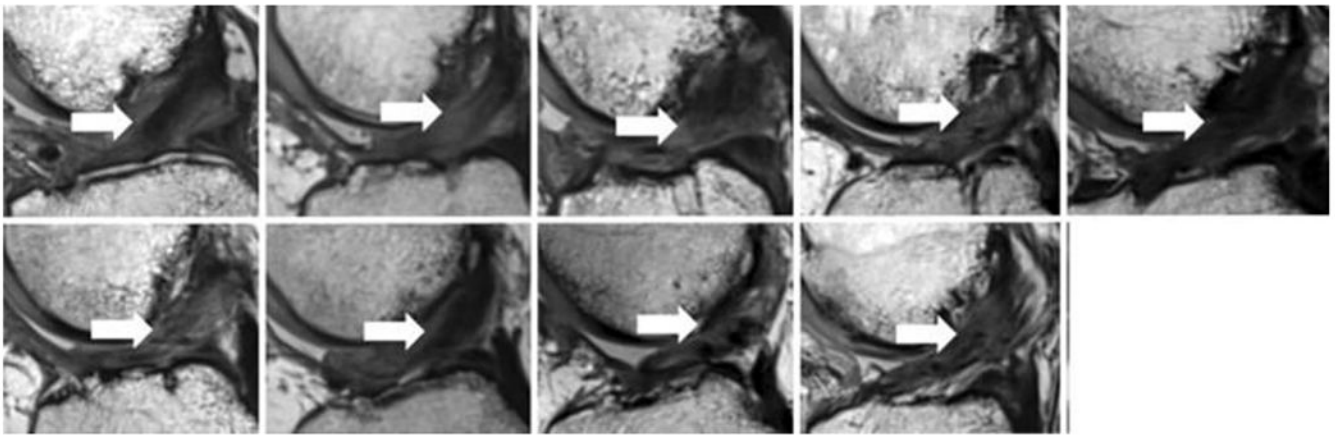

Figure 4:

Magnetic resonance imaging from 9 of the 10 patients in the scaffold enhanced repair group in the first-in-human study (sagittal view, 24 months after scaffold enhanced repair). All subjects had intact anterior cruciate ligament (ACL) fibers from the femoral to tibial attachment sites (arrows). The intact fibers have low signal intensity (black) reflecting highly organized tissue with little free water. (Used from Murray et al, OJSM, 2019[49]).

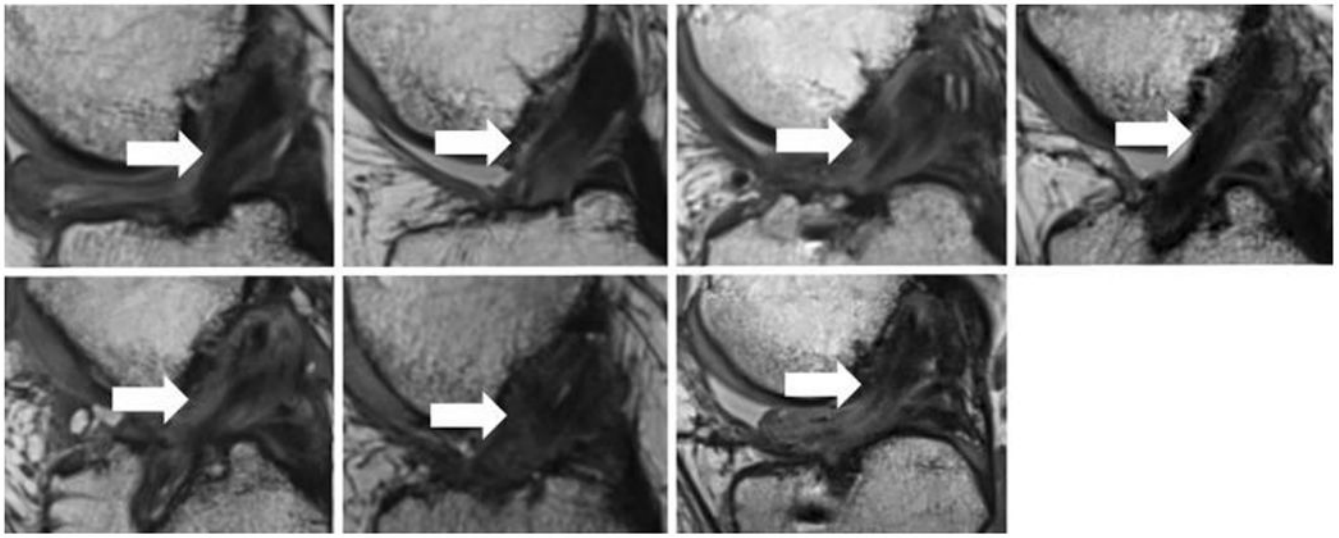

Figure 5:

Magnetic resonance imaging from 7 of the 10 patients in the autograft ACL reconstruction group in the first-in-human study (sagittal view, 24 months after ACL reconstruction). All subjects had intact grafts coursing from the femoral to tibial tunnels (arrows). The intact fibers have low signal intensity (black) reflecting highly organized tissue with little free water. (Used from Murray et al, OJSM, 2019[49]), with some variability among patients in the amount of highly organized tissue and less organized tissue in the region of the graft.

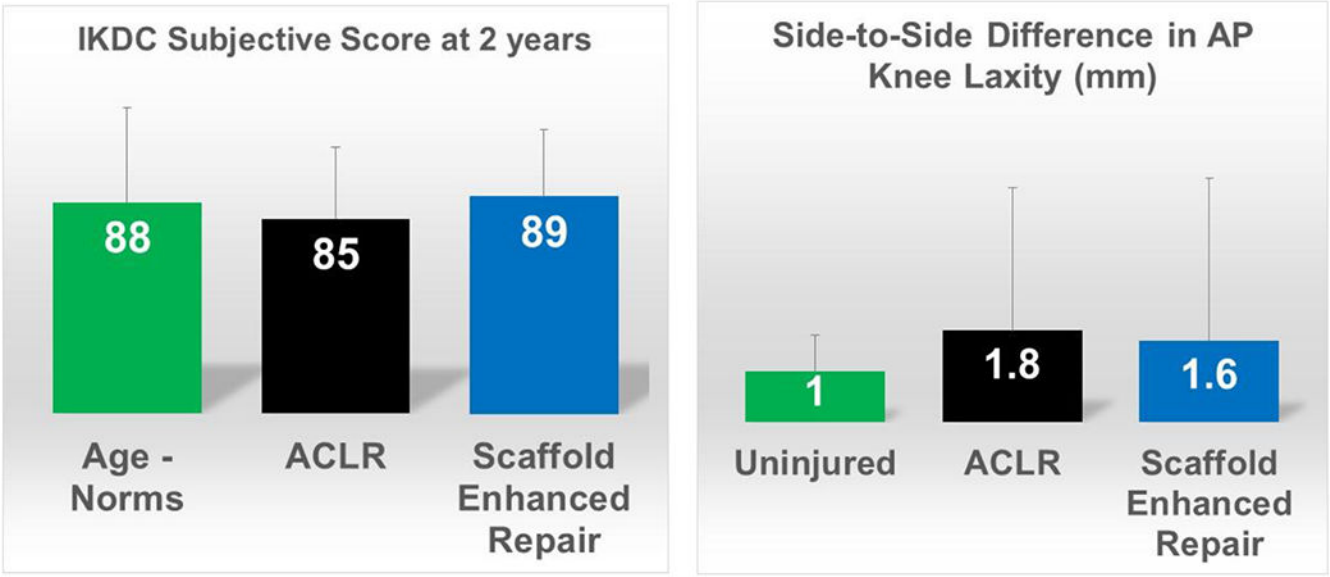

Figure 6:

Primary outcomes from the 100-patient randomized control trial of autograft ACL reconstruction vs scaffold enhanced repair in young, active patients, including the IKDC score and side-to-side difference in instrumented AP knee laxity measurements at 24 months after surgery. The age-matched norms for IKDC score have a mean of 88 points[52] and the mean difference in AP knee laxity for uninjured patients has been previously reported to be 1 mm.[53]