Systematic Review

Primary Repair of the Anterior Cruciate Ligament: A Systematic Review

Samuel A. Taylor, M.D., M. Michael Khair, M.D., Timothy R. Roberts, M.L.S., and Gregory S. DiFelice, M.D.

Purpose: To describe the clinical and preclinical research conducted on primary repair of the anterior cruciate ligament (ACL) during the past 10 years. **Methods:** A systematic search of PubMed, the Cochrane Central Register of Controlled Trials, and Embase was performed for all English-language studies published between 2003 and April 2014 on primary repair of the ACL. **Results:** Twenty-six studies met the inclusion and exclusion criteria. In the clinical research group, 8 studies (166 patients; age range, 10 to 71 years) met the inclusion and exclusion criteria and were largely long-term clinical outcome studies, based on the original cohorts from the 1970s and 1980s, and suggested high failure rates, additional surgery, and revision for instability. A subset of patients, however, achieved good to excellent subjective and objective long-term outcomes. In the preclinical research group, 18 studies met the inclusion and exclusion criteria and were based on an ACL transection model; they suggested that (1) stabilization of the knee with an internal suture strut improved the healing and biomechanical properties of the repaired ACL, (2) "enhancing" the repair with biological collagen-platelet composite augmentation improved healing and mechanical strength, (3) younger age and skeletal immaturity seem to correlate with improved histologic healing and biomechanical properties, (4) enhanced primary repair of the ACL may reduce post-traumatic osteoarthritis, and (5) the native ACL biomechanically outperformed the repaired ACL. **Conclusions:** Although long-term human studies suggest collectively unacceptable outcomes for open primary repair of the ACL, a subset of patients achieved acceptable long-term results. ACL transection model animal studies showed improved healing and biomechanics with primary suture repair stabilization, early intervention, biological augmentation techniques, and younger age. Primary repair of the ACL may be an effective treatment modality for an appropriately selected subset of patients. **Level of Evidence:** Level IV, systematic review of preclinical and clinical Level IV studies.

See commentary on page 2248

Primary ligamentous repair of the anterior cruciate ligament (ACL) was first reported over 100 years ago.[1] Mixed sentiments about the procedure's efficacy abounded in the previous century's literature.[2-5] Most recently, open primary ACL repair was largely abandoned in favor of other reconstructive options because of disappointing clinical outcomes at midterm follow-up.

Feagin et al.[6] popularized a technique in the 1970s that is archaic by today's standards. Patients underwent arthrotomy, suture repair through drill holes, and extensive postoperative cast immobilization. Feagin et al. reported 83% good to excellent results at 2 years postoperatively in a series of West Point cadets who underwent this procedure. The midterm results for the same cohort, however, were discouraging because of high rates of persistent symptoms including pain (71%), swelling (66%), and instability (94%). Furthermore, 75% of patients reported that their knee limited athletic activities, and 38% reported impairment of activities of daily living. These midterm findings introduced substantial doubt as to the procedure's legitimacy and durability.[7] Other studies that followed echoed the findings of Feagin et al. and delivered the deathblow to primary repair of the ACL.[8-10]

It should be noted that long-term clinical studies that reported ACL repair as ineffective were based on these original "failed" cohorts from the 1970s and 1980s and thus may not accurately reflect modern surgical acumen.[11-14] Therefore we ask the question: Could

From the Orthopaedic Trauma and Sports Medicine Services, Hospital for Special Surgery, New York, New York, U.S.A.

The authors report the following potential conflict of interest or source of funding: G.S.D. receives support from Arthrex.

Received December 4, 2014; accepted May 13, 2015.

Address correspondence to Gregory S. DiFelice, M.D., Orthopaedic Trauma Service, Hospital for Special Surgery, 535 E 70th St, New York, NY 10021, U.S.A. E-mail: difeliced@hss.edu

0749-8063/141021/$36.00

http://dx.doi.org/10.1016/j.arthro.2015.05.007

there still be a role for primary repair of the ACL among a highly selected group of patients? The purpose of this study was to describe the clinical and preclinical research conducted on primary repair of the ACL during the past 10 years. We hypothesized that human clinical outcome studies would be largely based on historical cohorts and that preclinical animal work would suggest a possible role for primary repair of the ACL.

Methods

A systematic literature review was conducted on primary repair of the ACL for studies in all languages published between 2003 and 2014. We performed literature searches in the PubMed database (April 18, 2014), Cochrane Central Register of Controlled Trials (April 18, 2014), and Embase database (April 18, 2014) to identify all studies that discussed the outcome of ACL repair based on the following criteria: (anterior cruciate ligament or ACL) AND repair AND (complications OR postoperative OR treatment outcome OR adverse effects.) Because the intent of the study was to look at the efficacy of primary ligamentous repair of the ACL using modern surgical techniques, we then limited the results to only those studies published between January 1, 2003, and April 18, 2014. The inclusion criteria included English language, human or animal in vivo studies, complete ACL tear, and primary repair of the ACL. The exclusion criteria included cadaveric studies, partial ACL tear, and healing response only without repair. After duplicates were removed, the initial search yielded 312 results for preliminary screening. The title of each study was reviewed as a first pass to exclude studies that discussed "reconstruction" as opposed to "repair." Two coauthors (S.A.T. and M.M.K.) independently reviewed abstracts and full-length articles for final application of the inclusion and exclusion criteria; discrepancies were discussed and overcome by consensus. Twenty-six studies met our inclusion criteria (8 clinical and 18 preclinical).

Results

Twenty-six studies found by our search met the inclusion and exclusion criteria (Fig 1). Eight involved human subjects and comprised the clinical studies (Tables 1-3). The remaining 18 involved animal models and comprised the preclinical studies (Table 4).

Clinical Studies

Four studies reported that primary ACL repair outcomes were unacceptable at long-term follow-up.[11-13,15] The primary repair technique that was used for these studies included arthrotomy, with a looped suture configuration that was secured in a transosseous fashion, with slight variations. Surgery was usually performed acutely, and the postoperative rehabilitation protocol called for at least 6 weeks of cast immobilization, with limited weight bearing up to 3 months after surgery.

Taylor et al.[13] reported on 34 of the 64 patients from the original cohort of Feagin et al.[6] at an average of 32 years' follow-up. On the basis of International Knee Documentation Committee scores, 53% of the cohort rated their knee as normal or nearly normal. The average Lysholm, Single Assessment Numeric Evaluation, and Tegner scores were 70.1, 68.9, and 3.7, respectively. Of the patients in this cohort, 28% ultimately underwent an additional procedure for persistent symptomatic instability. It is notable that 68% had Lysholm scores greater than or equal to 80.

Drogset et al.[12] presented their long-term prospective randomized data on 150 patients divided into 3 different treatment groups: (1) primary repair of the ACL (n = 33), (2) primary repair of the ACL with a ligament augmentation device, or (3) bone-tendon-bone (BTB) graft reconstruction. The Lysholm scores were better for the BTB graft reconstruction group at 16 years' follow-up (90.0 compared with 88.0 and 85.0). Of the primary repair patients, 52% had side-to-side KT-1000 differences (MEDmetric, San Diego, CA) less than 3 mm. On the basis of the Lysholm scores, 70% of patients who underwent primary repair of the ACL achieved good to excellent results. The 24% rate of conversion to reconstruction for repair patients was 10 times greater than that in patients who underwent BTB reconstruction (2%) ($P = .003$).

Strand et al.[11] reported on 81 patients treated with open primary repair of the ACL at 15 to 23 years' follow-up. Only 33% rated their knees as normal or nearly normal by the International Knee Documentation Committee rating, whereas 64% of knees were rated as good to excellent based on the Lysholm score. According to the subjective instability assessment, 56% of patients had no instability, 23% had instability during sports, and 21% had instability during activities of daily living. Side-to-side laxity testing with KT-1000 assessment was less than 3 mm for 41% of the cohort. Meunier et al.[15] reported similar outcomes between the 10 patients treated operatively in their study and the patients treated nonoperatively regarding demonstrable laxity, satisfaction, and progression of osteoarthritis.

Four other published studies also reported on patients who underwent primary ACL repair.[16-19] Arbes et al.[16] reported on a mixed cohort of 63 patients, of whom only 20 were available for follow-up and only 3 underwent primary repair of the ACL. Of these 3 patients, 2 ultimately underwent ACL reconstruction. The 1 remaining patient was reported to have a poor clinical outcome.

Gaulrapp and Haus[18] retrospectively reviewed cases of skeletally immature patients treated surgically for acute ACL rupture (primary repair, tibial eminence

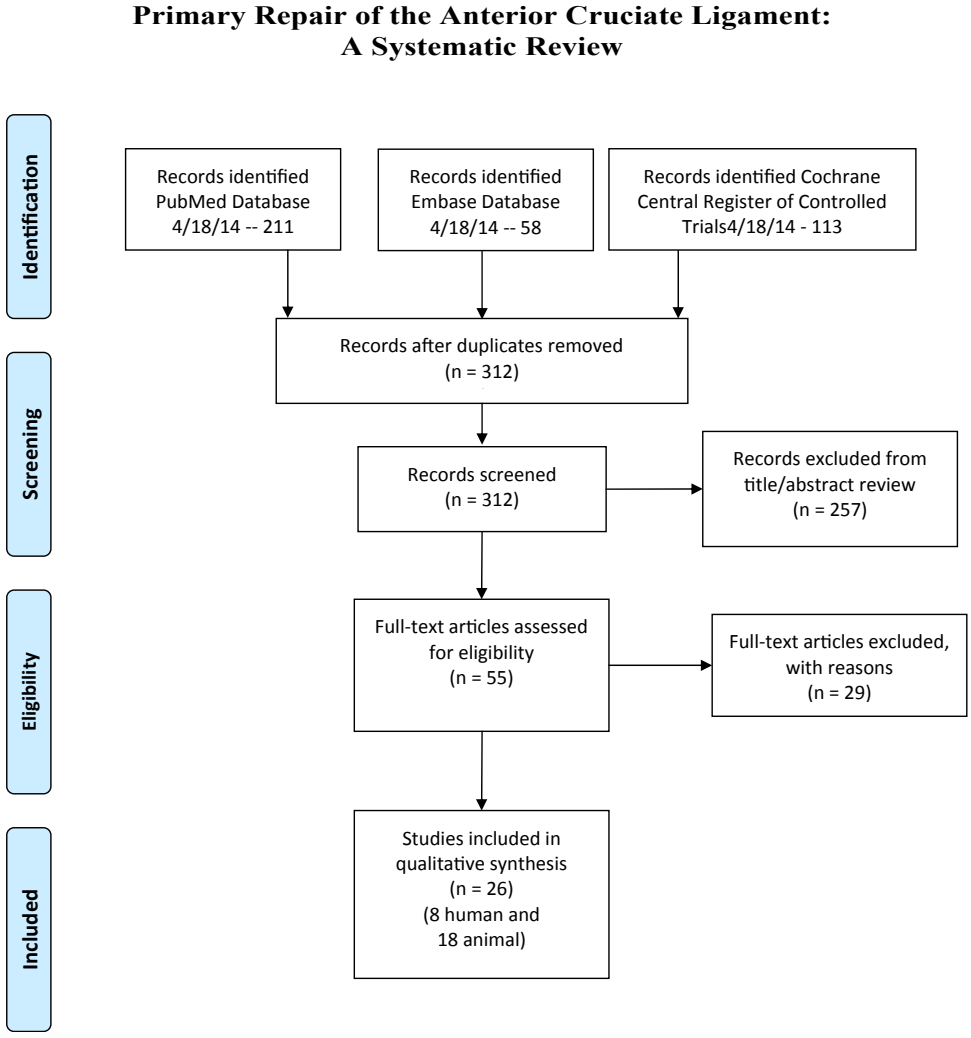

Fig 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart.

fixation, and reconstruction). An arthroscopic procedure was performed. Whereas the reconstructed group outperformed the repaired group regarding objective and subjective criteria, it should be noted that only 5 of the 24 patients who underwent primary repair of the ACL were available for follow-up.

Two case reports reported on arthroscopic primary repair of tibial-sided soft-tissue avulsions of the ACL.[17,19] One article reported a full, pain-free return to sports by 1 year postoperatively,[17] whereas the other reported favorable subjective and objective outcomes at 2 years postoperatively.[19]

Preclinical Studies

The preclinical studies identified by our search investigated both technical and biological solutions to improve healing during primary repair of the ACL. Several authors investigated the role of stability during ACL repair.[20-23] Seitz et al.[20] showed that stability obtained through an internal strut augmentation using a 3-mm polyethylene terephthalate (PET) band passed through femoral and tibial bone tunnels improved histologic evidence of healing when compared with the non-augmented repair construct. In their mountain sheep model, serial gross and histologic assessments were performed at varying time intervals up to 52 weeks. The mean cross-sectional area of the augmented group was significantly higher than that of the non-augmented group at all time points, but it never reached the cross-sectional area of the contralateral non-operated control ACL. Histologically, the augmented group showed more granulation tissue at 2 weeks, increased vascularity at 6 weeks, more fibroblasts and collagen at 16 weeks, more normal-appearing collagen alignment at 26 weeks, and well-defined longitudinally oriented collagen fascicles with sparse cellularity at 52 weeks. In their follow-up study using the same model, Seitz et al.[24] evaluated the biomechanical properties of primary repair augmented with the PET internal strut compared with suture repair

Table 1. Summary of Clinical Studies That Met Inclusion and Exclusion Criteria

Article	Technique	n	Mean Age at Index Procedure, yr (range)	Time to Follow-up, yr (range)	Comments
Strand et al.[11]	Arthrotomy, suture repair through transosseous tunnels (Palmer technique, n = 16; Marshall technique, n = 63)	81	28 (13-71)	— (15-23)	Cast immobilization for 6 wk Full weight bearing without crutches at 3 mo All operated on acutely
Drogset et al.[12]	Arthrotomy, multiple loop sutures through transosseous tunnels	33	29 (16-50)	16	Repair performed regardless of tear location Revision rate 10× higher for primary repair than BTB reconstruction ($P = .003$)
Gaulrapp and Haus[18]	Arthroscopic, suture repair through transphyseal tunnels	5	14 (10-16)	6.5	Only 5 of 24 primary repair patients were available for follow-up
Arbes et al.[16]	Arthroscopic, suture repair through transosseous tunnels	1	—	—	1 patient underwent primary repair and 2 patients underwent ACL reconstruction after primary repair Outcome details not clearly defined 43 of 63 who met inclusion criteria were lost to follow-up
Meunier et al.[15]	Arthrotomy, suture repair through transosseous tunnels	10	22 (14-30)	15 (14-19)	Long leg cast and non–weight bearing for 6 wk Concomitant meniscectomy in 60% No difference when compared with non-repaired control group
Taylor et al.[13]	Arthrotomy, suture repair through transosseous tunnels	34	20 (18-36)	32 (29-36)	Mean time to surgery, 10 d (range, 2-30 d) Cast immobilization Patients with proximal ACL avulsions had better results than those with midsubstance tears
Toy et al.[17]	Arthroscopic, primary repair of tibial-sided ACL tear with transtibial sutures	1	14	1	Skeletally immature
Ahn et al.[19]	Arthroscopic, primary repair of tibial-sided ACL avulsion tear with transtibial sutures	1	17	2	Concomitant partial lateral meniscectomy Splint/brace immobilization for 4 wk Full motion by 8 wk postoperatively

ACL, anterior cruciate ligament; BTB, bone-tendon-bone.

alone. They found that beginning at the 16-week time point, the PET-augmented primary repair group showed less instrumented laxity and greater tensile strength and ligament stiffness than the group that underwent suture repair alone ($P < .05$).

Murray et al.[23] tested a similar hypothesis that bone-to-bone (femur-to-tibia) suture fixation at the time of primary ACL repair would improve stabilization and lead to improved healing in a Yorkshire pig model with midsubstance ACL transection. They compared animals that underwent suture anchor primary repair with animals that underwent repair with transtibial suture augmentation. A bovine collagen–platelet-rich sponge aggregate ("enhanced repair") was used in both experimental groups. Although instrumented laxity was similar between the 2 repair groups, the transtibial suture–augmented group showed significantly higher yield load, maximum load, and stiffness compared with the non-augmented group.

In addition to mechanical augmentation, several groups have investigated the role of biologics in primary ACL repair including the use of a collagen scaffold[25-29] and platelet-rich plasma (PRP).[30-33] Fleming et al.[25] reported that augmentation with a bovine collagen scaffold alone did not improve the biomechanical properties of a repaired porcine ACL. More specifically, no statistically significant differences were detected for anteroposterior laxity at 30°, 60°, or 90°, nor were there any differences between the 2 groups for yield load, maximum failure load, linear stiffness, displacement to yield, displacement to failure, or displacement to 5 N of tensile load. In addition, the histologic analysis findings were comparable between the 2 groups. Joshi et al.,[26] however, showed that the addition of platelets to this collagen composite scaffold did improve both yield loads and linear stiffness at the 3-month post-procedure time point. In addition, histologic analysis showed significantly increased cellularity for the collagen-platelet composite (CPC)–augmented repair compared with the non-augmented group. Palmer et al.[28] looked at the effect of warming such a CPC on ACL properties after primary repair. In the 5 female Yorkshire pigs euthanized at 14 weeks after the procedure, the authors determined that increased

Table 2. Summary of Clinical Studies' Subjective Outcomes

Article	IKDC	Lysholm	Tegner	KOOS	SANE	Other
Strand et al.[11]	33% normal or near normal A in 6% B in 27% C in 46% D in 21%	64% good or excellent Median score, 88 Excellent in 33% Good in 31% Fair in 25% Poor in 11%	—	—	—	Sense of instability (56% none, 23% with sport, 21% with ADLs)
Drogset et al.[12]	—	77% good to excellent Mean at 5 yr, 88.3 Mean at 16 yr, 88.0	Mean at 5 yr, 5.0 Mean at 16 yr, 5.1	—	—	Subjective knee function: 85% good to excellent at 16 yr
Gaulrapp and Haus[18]	40% nearly normal A in 0% B in 40% C in 60%	Mean, 80	Mean, 2.7	—	—	—
Arbes et al.[16]	—	—	—	Pain: 86 Symptoms: 75 Quality of life: 82 Sports: 80 ADL function: 100	—	—
Meunier et al.[15]	—	70% good to excellent	Mean, 5.0	Pain: 80 Symptoms: 71 Quality of life: 58 Sports: 62 ADL function: 92	—	50% satisfied with activity level
Taylor et al.[13]	41% normal or near normal A in 12% B in 29% C in 29% D in 29%	Mean, 70.1	Mean, 3.7	Pain: 77 Symptoms: 68 Quality of life: 57 Sports: 56 ADL function: 83	Mean, 68.9	—
Toy et al.[17]	—	—	—	—	—	"Pain free"
Ahn et al.[19]	90	95	—	—	—	—

ADL, activity of daily living; IKDC, International Knee Documentation Committee; KOOS, Knee Injury and Osteoarthritis Outcome Score; SANE, Single Assessment Numeric Evaluation.

warming of the CPC adversely affected the ultimate biomechanical properties of the repaired ligament. Furthermore, the volume and maximum and minimum cross-sectional area were inversely related to the injection temperature as determined by magnetic resonance imaging.

Fisher et al.[27] used 16 skeletally mature goats to show that porcine extracellular matrix bioscaffold and hydrogel improve the healing and biomechanical properties of the transected ACL. The animals were divided into 3 experimental groups: sham operation, suture repair only, and suture repair with extracellular matrix augmentation. At the 12-week time point, a similar cross-sectional area was found between the sham surgery group and extracellular matrix–augmented group, which was in turn 4.5 times greater than the cross-sectional area of the suture repair–alone group. The augmented group achieved 48% of the stiffness of the sham group, and stiffness in the augmented group was 2.4 times greater than that in the suture repair–only group.

Introduction of a collagen scaffold does not seem to generate an adverse inflammatory response. Magarian et al.[29] looked at markers of systemic and local inflammatory response in 18 skeletally immature Yorkshire pigs that were divided into 3 experimental groups: suture repair alone, suture repair augmented with a collagen sponge, and suture repair augmented with a CPC. No significant differences were found regarding synovial thickening, joint effusion, synovial leukocyte counts, or peripheral leukocyte counts among the 3 experimental groups when compared with contralateral control knees.

PRP may be a useful augmentation tactic during primary ACL repair. Whereas Murray et al.[31] found similar cross-sectional areas between ACLs treated with suture repair and those treated with suture repair and collagen-PRP augmentation, they reported significant biomechanical differences. Yield load, maximum load, and linear stiffness were significantly improved in the augmented group compared with the non-augmented group ($P < .05$). Furthermore, the location of failure

Table 3. Summary of Clinical Studies' Objective Outcomes

Article	Examination	KT	Osteoarthritis	Additional Surgery	Other
Strand et al.[11]	Positive pivot-shift test in 25%	<3 mm in 41% 3-5 mm in 36% >5 mm in 21%	IKDC A in 25% B in 62% C in 13% D in 2%	13% underwent reoperation for instability 7.5% underwent reoperation for meniscus	No subjective instability in 57% Subjective instability with physical activity in 21% and with ADLs in 22%
Drogset et al.[12]	Extension deficit >5° in 5% at 5 yr and 30% at 16 yr Positive pivot-shift test in 51% at 5 yr and 18% at 16 yr Positive Lachman test in 44% at 5 yr and 18% at 16 yr	Mean, 1.9 mm at 16 yr <3 mm in 52% and >3 mm in 48%	Ahlbäck grade 0 in 83%	24% revision rate	—
Gaulrapp and Haus[18]	—	Mean, 2.6 mm	Radiographic OA in 60%	—	—
Arbes et al.[16]	Positive Lachman test	Mean instrumented laxity, 11 mm	—	—	—
Meunier et al.[15]	Positive pivot-shift test in 60% Positive Lachman test in 70%	Mean, 2.8 mm <3 mm in 25% and >3 mm in 75%	30% without OA	20% underwent revision for instability	—
Taylor et al.[13]	—	—	—	64% underwent additional procedures 28% underwent revision for instability	—
Toy et al.[17]	Negative Lachman test Negative pivot-shift test	—	—	—	Full return to sports
Ahn et al.[19]	Negative Lachman test Negative pivot-shift test Full ROM	2 mm	—	—	Continuity of ACL fibers on MRI at 6 mo

ACL, anterior cruciate ligament; ADLs, activities of daily living; IKDC, International Knee Documentation Committee; MRI, magnetic resonance imaging; OA, osteoarthritis; ROM, range of motion.

during load-to-failure analysis was always at the experimental transection site among the suture repair—only group, whereas failure occurred at the bone-tendon interface in 40% of specimens (2 of 5) in the augmented repair group.

Although the addition of PRP to the collagen sponge appeared to improve the mechanical and histologic properties of the repaired ACL, Murray et al.[32] showed that PRP augmentation without a collagen sponge during primary suture repair of the ACL did not improve anteroposterior laxity, linear stiffness, maximum load, displacement at failure, or energy to failure between the 2 groups. Furthermore, it appeared that the PRP concentration did not affect the mechanical outcomes. In a Yucatan mini-pig model, Murray and colleagues[33] compared primary suture repair, bone-to-bone suture augmentation, and collagen scaffold with PRP. The only variable was the concentration of PRP (5× on one side and 3× on the contralateral side). Although histologic evaluation did show a statistically significant 24.1% decrease in cellular density of the repair tissue in the 3× PRP concentration group at 13 weeks after the procedure, biomechanical testing findings were statistically equivalent between the 2 groups regarding yield loads, stiffness, and mean anteroposterior knee laxity at 30° and 90°.

Age and skeletal maturity may affect healing potential after ACL primary repair. Murray et al.[34] showed that immature animals had a more robust functional healing response than mature animals. Twenty-one Yucatan mini-pigs of varying levels of skeletal maturity underwent transection of the bilateral ACL either with enhanced suture repair with CPC augmentation or left as a control without intervention. The results suggested that, when mechanical outcomes were normalized by the intact values for each group, the juvenile group achieved a significantly higher percentage of intact yield load than the skeletally mature group (25% *v* only 7%) ($P < .01$) and linear stiffness for the adolescent group trended toward twice that for the adult group ($P = .09$). Furthermore, the authors suggested age-dependent biomechanical results. Yield loads in the adolescent pigs were 68% greater than those in the adult group ($P < .01$). Adverse effects regarding

Table 4. Summary of Preclinical Animal Studies

Article	Purpose	n	Animals	Methods	Time to Sacrifice	Outcome Measures	Comments
Murray et al.[31]	Evaluate effect of repair augmentation with collagen–PRP hydrogel scaffold augmentation on healing and biomechanical properties	5 (bilateral)	Skeletally immature female Yorkshire pigs	Bilateral knees used: 1. Suture repair 2. Contralateral suture repair and augmentation with provisional scaffold (collagen–PRP hydrogel)	4 wk	No significant dimension differences between 2 experimental groups by MRI Augmented suture repair group with increased load at yield, maximum load, and tangent modulus ($P <$ .05) compared with suture repair alone Augmented repair biomechanically inferior to intact control	ACL transection midsubstance
Seitz et al.[20]	Evaluate effect of repair augmentation with internal strut on healing	20	Female mountain sheep	Randomized into 2 groups: 1. Suture repair only (n = 10) 2. Suture repair with augmentation with PET band (n = 10)	2, 6, 16, 26, and 52 wk	Histology: PET augmentation decreased healing time when compared with non-augmented group and also protected repair from necrosis	ACL transection at femoral attachment No biomechanical data
Murray et al.[32]	Evaluate effect of repair augmentation with PRP alone on structural properties of ACL	6 (bilateral)	Skeletally immature female Yorkshire pigs	Bilateral knees used: 1. Suture repair 2. Contralateral suture repair with injection of 3 mL of PRP at transection site	14 wk	No significant biomechanical improvements in AP laxity, maximum tensile load, or linear stiffness achieved by adding PRP compared with suture repair alone	ACL transected at junction of proximal and middle thirds
Palmer et al.[28]	Determine if temperature of injected CPC affects mechanical properties of repaired ACL	5 (bilateral)	Female Yorkshire pigs	Bilateral knees used: 1. Suture repair with collagen sponge alone 2. Contralateral suture repair with collagen sponge and CPC injected at varying temperatures (28°C to 33°C)	14 wk	Temperature was inversely proportional to biomechanical properties of healing ACL and cross-sectional area by MRI (higher-temperature injection led to biomechanically weaker construct with reduced cross-sectional area)	ACL transection at junction of proximal and middle thirds

(continued)

Table 4. Continued

Article	Purpose	n	Animals	Methods	Time to Sacrifice	Outcome Measures	Comments
Joshi et al.[26]	Evaluate effect of repair augmentation with bioactive (CPC) scaffold on structural properties of ACL	18 (27 knees)	Skeletally immature female Yorkshire pigs	Bilateral knees used: 1. Suture repair alone 2. Contralateral suture repair with collagen sponge and CPC augmentation	4, 6, and 12 wk	Augmentation with CPC improved yield loads and linear stiffness at final 3-mo follow-up compared with suture repair alone ($P < .05$) No significant difference in cross-sectional area between 2 groups based on MRI Higher cellularity (25.5%) within CPC-augmented group at 3 mo ($P = .015$)	ACL transection midsubstance
Murray et al.[23]	Determine whether bony stabilization between tibia and femur improves structural properties after ACL repair	12	Skeletally immature female Yorkshire pigs	Randomized into 2 groups: 1. Traditional Marshall suture repair 2. Enhanced repair with sutures tied directly to tibia through transosseous tunnel	15 wk	Bone-to-bone fixation significantly improved yield load, maximum load, and stiffness compared with traditional suture –only repair ($P < .05$)	ACL transection midsubstance
Murray et al.[34]	Assess effect of age on functional healing properties after primary repair of ACL	8 juvenile (bilateral) 8 adolescent (bilateral) 5 adult (bilateral)	Yucatan mini-pigs	Bilateral knees used: 1. Untreated transected ACL 2. Contralateral suture repair enhanced with CPC	15 wk	Younger animals had improved structural properties of both repaired and unrepaired ACL Maximum load never exceeded 35% of intact ACL regardless of age or repair	ACL transection through proximal third Augmented with bone-to-bone fixation using absorbable sutures
Fleming et al.[25]	Evaluate effect of repair augmentation with collagen composite scaffold alone (without platelets) on structural properties of ACL	8 (bilateral)	Yucatan mini-pigs	Bilateral knees used: 1. Suture repair alone 2. Contralateral suture repair with collagen composite sponge alone (without platelets)	18 wk	Augmentation with collagen composite sponge alone did not significantly improve functional properties of repaired ACL	ACL transected at junction of proximal and middle thirds Augmented with bone-to-bone fixation using absorbable sutures
Magarian et al.[37]	Assess effect of surgical delay on structural properties of repaired ACL	16 (staged bilateral)	Skeletally immature female Yorkshire pigs	All animals underwent enhanced primary repair of ACL Bilateral ACL transection at time 0 with immediate ACL repair of 1 knee Contralateral knees randomized into 2 groups: 1. Early repair group: 2 wk after transection 2. Late repair group: 6 wk after transection	15 wk	2-wk delayed repair resulted in 40% reduction of yield load ($P = .01$) 6-wk delayed repair resulted in 60% decrease of yield load ($P = .01$) Maximum load and linear stiffness negatively affected by delayed surgical repair ($P = .011$)	ACL transected at junction of proximal and middle thirds Augmented with bone-to-bone fixation using absorbable sutures Augmented with CPC

(continued)

Table 4. Continued

Article	Purpose	n	Animals	Methods	Time to Sacrifice	Outcome Measures	Comments
Vavken et al.[35]	Determine if mechanical properties of repaired ACL correlate with VEGF receptors' messenger RNA expression and if age influences this association	19 (bilateral)	Female Yucatan pigs (aged 1-33 mo, distribution not specified)	Bilateral knees used: 1. Enhanced primary repair of ACL 2. ACL transection without repair RT-PCR to evaluate VEGF receptor (1 and 2) expression after animal sacrifice	15 wk	VEGF receptor 1 expression was associated with increased displacement to yield and failure ($P < .01$) No significant association with VEGF receptor expression and stiffness, maximum load, or yield load Age negatively affected yield load ($P = .03$), maximum load ($P = .04$), and stiffness ($P = .03$)	ACL transected at junction of proximal and middle thirds Augmented with bone-to-bone fixation using absorbable sutures Augmented with CPC
Mastrangelo et al.[33]	Determine if platelet concentration affects structural properties of ACL after repair	8 (bilateral)	Adolescent Yucatan mini-pigs (5 male, 3 female)	All animals underwent bilateral enhanced primary repair of ACL Bilateral knees used: 1. Augmentation with PRP 5× baseline systemic platelet count 2. Augmentation with PRP 3× baseline systemic platelet count	13 wk	3× PRP concentration resulted in 24% decrease in cellularity No significant biomechanical (yield load, stiffness, and AP laxity at 30° and 90°) differences found between 2 experimental groups	ACL transected at junction of proximal and middle thirds Augmented with bone-to-bone fixation using absorbable sutures Augmented with CPC (PRP concentration was variable)
Haus et al.[36]	Determine effect of ACL primary repair on uninjured ligament insertion site	8 juvenile (bilateral) 8 adolescent (bilateral) 8 adult (bilateral)	Yucatan mini-pigs	Bilateral knees used: 1. Enhanced primary repair of ACL 2. ACL transection without repair	1, 2, 4, and 15 wk	ACL insertion site histology: Juvenile and adolescent animals showed fibroblast proliferation, return of collagen alignment, and early (2-4 wk) osteoclastic resorption of fibrocartilage zone that partially reappeared by week 15 Adult animals showed persistent loss of collagen alignment and chondrocyte disorganization	ACL transected at junction of proximal and middle thirds Augmented with bone-to-bone fixation using absorbable sutures Augmented with CPC (PRP concentration was variable)

(continued)

Table 4. Continued

Article	Purpose	n	Animals	Methods	Time to Sacrifice	Outcome Measures	Comments
Fisher et al.[27]	Examine potential advantages of using ECM bioscaffolds to heal transected ACL	16	Skeletally mature female Spanish breed goats	Randomized into 2 groups: 1. Suture repair only 2. Suture repair and augmentation with ECM hydrogels from small intestine of knockout pig (Gal-Safe, Revivicor Inc, Blacksburg, VA) Sham surgery performed on contralateral ACL (surgically visualized but not disrupted)	12 wk	Cross-sectional area was similar between ECM-augmented and sham groups, which were both 4.5× greater than suture repair only ($P < .05$) Stiffness 2.4× greater in ECM-augmented group than suture-only group ($P < .05$)	ACL transected midsubstance No bone-to-bone suture augmentation
Magarian et al.[29]	Assess systemic and local inflammatory response to bioscaffold augmentation during primary repair of ACL	18	Skeletally immature female Yorkshire pigs	Randomized into 3 groups: 1. Suture repair only (n = 6) 2. Suture repair and augmentation with collagen sponge (n = 6) 3. Suture repair and augmentation with CPC (n = 6)	15 wk	No difference in synovial thickening, effusion, synovial cell count, and peripheral leukocyte count among 3 groups	ACL transected at junction of proximal and middle thirds No bone-to-bone suture augmentation
Vavken et al.[38]	Compare biomechanical outcomes between bioenhanced ACL primary repair and BTB reconstruction	24	Skeletally immature female Yorkshire pigs	Randomized into 3 groups: 1. ACL transection without intervention (n = 8) 2. Enhanced suture repair and augmentation with CPC (n = 8) 3. ACL reconstruction with BTB allograft (n = 8)	15 wk	AP laxity testing was similar between reconstruction and repair groups and was 3 mm less than in group that underwent transection without treatment at 30° and 60° of flexion ($P < .05$) Biomechanical testing (displacement and load) were also statistically similar between reconstruction and repair but different from transection-alone group ($P < .05$)	ACL transected at junction of proximal and middle thirds Enhanced repair included bone-to-bone augmentation fixation using absorbable sutures and CPC

(continued)

Table 4. Continued

Article	Purpose	n	Animals	Methods	Time to Sacrifice	Outcome Measures	Comments
Murray and Fleming[39]	Assess long-term effects of enhanced primary repair of ACL on development of post-traumatic osteoarthritis	64	Late adolescent Yucatan mini-pigs	Randomized into 4 groups: 1. ACL transection without repair (n = 16) 2. ACL reconstruction with BTB allograft (n = 16) 3. Bioenhanced ACL reconstruction (BTB allograft and bioactive scaffold) (n = 16) 4. Bioenhanced ACL repair	6 mo (n = 8 from each experimental group) 12 mo (n = 8 from each experimental group)	Biomechanical outcomes (linear stiffness, yield, and maximum load) were similar among enhanced primary repair, reconstruction, and enhanced reconstruction groups Osteoarthritic changes were significantly less for enhanced primary repair than in untreated transection or enhanced reconstruction groups ($P < 0.05$) at 12 months postoperative time point	ACL transected at junction of proximal and middle thirds Enhanced repair included bone-to-bone augmentation fixation with absorbable sutures and CPC Enhanced reconstruction included addition of CPC
Nguyen et al.[43]	Assess biomechanical implications of new locking suture technique and bioscaffold on primary repair of ACL	10	Skeletally mature female Dutch milk goats	Randomized into 2 groups: 1. ACL suture repair only (n = 5) 2. ACL suture repair with SIS augmentation (n = 5)	12 wk	No difference between 2 repair groups for cross-sectional area, stiffness, or instrumented laxity Both experimental groups showed less cross-sectional area, less stiffness, and greater laxity than intact control ACL	ACL transection midsubstance Used locking suture configuration within ACL stumps that were tied over transection site No bone-to-bone suture augmentation Reported results and authors' conclusions do not align
Seitz et al.[24]	Evaluate long-term (12-mo) effect of repair augmentation with internal strut on healing	40	Adult female mountain sheep	Randomized into 2 groups: 1. Suture repair only (n = 20) 2. Suture repair with augmentation with PET band (n = 20)	2, 6, 16, 26, and 52 wk	Beginning at 16-wk time point, PET-augmented primary repair showed less laxity and greater tensile strength and ligament stiffness than suture repair alone ($P < .05$)	ACL transection at femoral attachment No biomechanical data

ACL, anterior cruciate ligament; AP, anteroposterior; BTB, bone-tendon-bone; CPC, collagen-platelet composite; ECM, extracellular matrix; MRI, magnetic resonance imaging; PET, polyethylene terephthalate; PRP, platelet-rich plasma; RT-PCR, reverse transcription polymerase chain reaction; SIS, small intestinal submucosa; VEGF, vascular endothelial growth factor.

maximal load, stiffness, and anteroposterior laxity at 90° of flexion also occurred in an age-dependent manner. Another study examined the expression of vascular endothelial growth factor receptor expression among fibroblasts after enhanced primary repair of the ACL in a porcine model that included animals of variable ages (1 to 33 months).[35] Vascular endothelial growth factor receptor 1 was associated with increased displacement to yield and displacement to failure ($P < .01$) but not with stiffness, maximum load, or yield load. Age negatively affected yield load, maximum load, and stiffness ($P < .05$).

Haus et al.[36] evaluated the age-dependent cellular response at the insertion site during primary repair of the ACL in a porcine model with 3 different age groups (skeletally immature, adolescent, and adult). Although no significant differences were identified regarding leukocyte counts among any of the age groups, significantly more fibroblastic proliferation, osteoclast activity, and angiogenesis were reported for the skeletally immature and adolescent animals compared with the adult group.

Magarian et al.[37] showed that delaying the time to primary ACL repair in a porcine model has a detrimental effect on functional performance. A group of Yorkshire pigs underwent bilateral enhanced primary repair of their ACLs in a staged fashion. The ACLs were transected and then subsequently treated with enhanced primary repair at either 2 weeks or 6 weeks after transection. The contralateral ACL underwent transection with immediate, concomitant, enhanced repair and was used as a control. In vivo biomechanical testing at 15 weeks after repair showed significantly decreased yield loads of 40% and 60% for ACLs treated with repair after 2- and 6-week delays, respectively, when compared with immediate repair. Maximum load, linear stiffness, and anteroposterior laxity at 30° of flexion were also adversely affected ($P < .05$).

Vavken et al.[38] reported equivalent results regarding biomechanical properties for primary ACL repair with CPC and allograft ACL ligament reconstruction in a porcine model. They randomly assigned 24 skeletally immature pigs to 1 of 3 groups: enhanced primary repair, BTB allograft, or transection without intervention. They found superiority of both repair and reconstruction to no intervention. Furthermore, they reported that there were no significant biomechanical differences between the repair and reconstruction groups at the 15-week time point.

Murray and Fleming[39] published the long-term results (6 months and 12 months) of both biomechanical properties and magnitude of post-traumatic osteoarthritis associated with various treatments in an ACL transection model. They used 64 Yucatan mini-pigs and divided them into 4 experimental treatment groups (transection without intervention, ACL reconstruction with BTB allograft, ACL reconstruction with BTB allograft and CPC augmentation, and bioenhanced primary repair of the ACL). Half of the animals from each group were euthanized at 6 months and the remaining half at 12 months postoperatively. The authors found comparable biomechanical results among the reconstruction, enhanced reconstruction, and enhanced primary repair groups, which were all significantly improved compared with the group that underwent transection without intervention. Furthermore, they showed that the incidence of post-traumatic osteoarthritis was significantly less in the enhanced primary repair group compared with either the reconstruction group or the group that underwent transection without intervention ($P < .05$) and the enhanced primary repair group strongly trended toward less osteoarthritis than the enhanced reconstruction group ($P = .068$).

Discussion

Historical clinical data suggest that open primary repair of the ACL has an unacceptably high failure rate. Recent long-term clinical follow-up studies confirm this notion. However, after a thorough systematic review of the clinical studies published on this topic, we have shown that a subset of patients in these studies did, in fact, have subjective and objective success, and the only study that analyzed outcomes by tear type suggested that better outcomes were noted more frequently with proximal tears with excellent tissue quality. Preclinical animal studies evaluating a midsubstance repair model suggest that enhanced stabilization of the knee during the early postoperative period with an internal suture strut, augmentation with CPC, early intervention, and patient selection (younger age) may improve the healing and biomechanical properties of the repaired ACL and reduce post-traumatic osteoarthritis. Future studies are needed to identify patients who may benefit from primary repair of the ACL.

On first review, long-term human clinical outcome studies report unacceptably high failure rates and overwhelmingly suggest that primary repair of the ACL is an inadequate treatment option. Long-term follow-up studies report fair or poor results in nearly 30% of patients,[11,12] as well as high rates of additional surgery (64%)[13] and revision to ACL reconstruction for instability (13% to 24%).[11-13] In addition, objective long-term data show excessive laxity (>5 mm) by KT-1000 assessment in 21% of these patients.[11] As a result, there has been an academic and clinical exodus from primary repair toward modern methods of ligament reconstruction.

On second review, however, it is clear that a subset of patients in these same studies did meet the criteria for clinical success. In fact, 33% of patients had excellent Lysholm scores and 41% of patients had final instrumented laxity measurements of less than 3 mm.[11]

Although their numbers were small, Gaulrapp and Haus[18] did show—in 5 skeletally immature patients with proximal femoral avulsion tears repaired primarily—KT-1000 measurements of less than 3 mm compared with the contralateral side. The original cohorts from which the long-term human data emanate were typically mixed cohorts including patients with concomitant knee injuries and widely varied age groups and, perhaps more importantly, did not discriminate by tear pattern or location. The luxuries of preoperative magnetic resonance imaging and/or diagnostic arthroscopy were not commonly available during this time. Furthermore, modern surgical techniques and hardware such as arthroscopy and suture anchors were not yet available.

One of the landmark studies on primary ACL repair that supported the transition from primary repair to ACL reconstruction[40] should be reviewed here for perspective. The authors were the only group to perform subgroup analysis by age, sex, and activity level/sport, and most importantly, they differentiated tears by tissue quality, tear location (proximal to distal), and overall knee laxity. They noted that type I tears (proximal) with good tissue quality were more common among skiers and that these tears trended toward improved outcomes. They correlated a football mechanism of injury and midsubstance (type IV) tears with poor postoperative outcomes. Although their overall outcomes were considered unacceptable and contributed to the widespread abandonment of ACL repair, it should be noted that a subset of patients did achieve excellent outcomes with this approach. This raises an interesting question: Can modern diagnostic modalities enable us to identify a subset of patients who would benefit from primary repair of the ACL?

Although we excluded 2 studies on healing response from this systematic review because they are not considered to have used formal repair techniques,[41,42] they contribute value to the overall discussion on primary ACL repair, particularly regarding tear location. Steadman et al.[42] used an arthroscopic awl to produce 6 to 10 holes in the cortical bone of the femoral ACL footprint to create a "healing response." Surgery was performed early (mean of 22 days after injury). All patients were skeletally immature, and all had proximal one-third ACL disruptions. Three patients had subsequent reinjury at 42 months after treatment requiring reconstruction. The results for the remaining 10 patients at 69 months after healing-response therapy showed an improvement in the average KT-1000 difference from 5 mm (range, 3 to 10 mm) preoperatively to 2.6 mm (range, 0 to 4 mm). All patients considered their knee function normal, with an average patient satisfaction score of 9.9 (on a 10-point scale).

Given the aforementioned findings, it is important that we consider the effect of age, surgical technique, and tear location on healing and biomechanics after primary ACL repair. In light of the perceived human failure with primary repair of the ACL, the bulk of the literature over the preceding decade used animal models to assess both the technical and biological aspects of healing.

Murray et al.[34] recently showed an age-dependent healing response in a porcine model at 15 weeks postoperatively. The juvenile pigs reached 25% of the intact control's yield load, whereas the skeletally mature group reached only 7% of its intact yield load ($P < .01$). Yield loads in the adolescent pigs were 68% greater than those in the adult group ($P < .01$). Adverse effects regarding maximal load, stiffness, and anteroposterior laxity at 90° of flexion also occurred in an age-dependent manner. Haus et al.[36] showed higher concentrations of reparative cells such as fibroblasts and osteoclasts, as well as blood vessels, in the immature group compared with the mature group in their porcine model. Although it remains to be determined whether these findings occur in humans, it may be an important consideration.

Stabilization of the repaired ligament, with an internal strut femur-to-tibia suture, is likely protective and may allow improved healing.[20-23] Furthermore, other studies stressed the importance of providing a suitable biological environment by adding a collagen matrix sponge[25-29] or PRP to stimulate healing.[30-33] The literature suggests a mutually inclusive relation between collagen matrix sponge and PRP. That is, augmentation with a collagen scaffold[25] or PRP[32] in isolation did not improve biomechanical or histologic properties, but combining these materials did positively affect healing.[30,31]

Appropriate patient selection and improved surgical techniques may resurrect ACL primary repair and enable a transition from preclinical studies to clinical implementation. We would reinforce the importance of patient selection; in particular, proximal tears may be most amenable to primary repair. Future translational studies are needed to identify patients who may benefit from primary repair of the ACL and advance our collective surgical acumen.

Limitations

The limitations of this systematic review correlate with those of the constituent studies. Clinical studies were largely long-term historical outcome studies whose patients represented all comers rather than a preselected subset. Furthermore, these patients were not privy to modern diagnostic modalities, preoperative and postoperative rehabilitation protocols, or minimally invasive surgical techniques and reliable fixation devices. Interpretation of preclinical studies is limited by variability of species selection and heterogeneity of surgical techniques.

Conclusions

Although long-term human studies suggest collectively unacceptable outcomes for open primary repair of the ACL, a subset of patients achieved acceptable long-term results. ACL transection model preclinical studies showed improved healing and biomechanics with primary suture repair stabilization, early intervention, biological augmentation techniques, and younger age.

References

1. Robson AW. VI. Ruptured crucial ligaments and their repair by operation. *Ann Surg* 1903;37:716-718.
2. Liljedahl SO, Lindvall N, Wetterfors J. Early diagnosis and treatment of acute ruptures of the anterior cruciate ligament; a clinical and arthrographic study of forty-eight cases. *J Bone Joint Surg Am* 1965;47:1503-1513.
3. O'Donoghue DH. An analysis of end results of surgical treatment of major injuries to the ligaments of the knee. *J Bone Joint Surg Am* 1955;37:13;passim.
4. Pringle JH. I. Avulsion of the spine of the tibia. *Ann Surg* 1907;46:169-178.
5. England RL. Repair of the ligaments about the knee. *Orthop Clin North Am* 1976;7:195-204.
6. Feagin JA, Abbott HG, Roukous JA. The isolated tear of the ACL. *J Bone Joint Surg Am* 1972;54:1340 (abstract).
7. Feagin JA Jr, Curl WW. Isolated tear of the anterior cruciate ligament: 5-year follow-up study. *Am J Sports Med* 1976;4:95-100.
8. Odensten M, Lysholm J, Gillquist J. Suture of fresh ruptures of the anterior cruciate ligament. A 5-year follow-up. *Acta Orthop Scand* 1984;55:270-272.
9. Engebretsen L, Benum P, Sundalsvoll S. Primary suture of the anterior cruciate ligament. A 6-year follow-up of 74 cases. *Acta Orthop Scand* 1989;60:561-564.
10. Warren RF. Primary repair of the anterior cruciate ligament. *Clin Orthop Relat Res* 1983;(172):65-70.
11. Strand T, Molster A, Hordvik M, Krukhaug Y. Long-term follow-up after primary repair of the anterior cruciate ligament: Clinical and radiological evaluation 15-23 years postoperatively. *Arch Orthop Trauma Surg* 2005;125:217-221.
12. Drogset JO, Grontvedt T, Robak OR, Molster A, Viset AT, Engebretsen L. A sixteen-year follow-up of three operative techniques for the treatment of acute ruptures of the anterior cruciate ligament. *J Bone Joint Surg Am* 2006;88:944-952.
13. Taylor DC, Posner M, Curl WW, Feagin JA. Isolated tears of the anterior cruciate ligament: Over 30-year follow-up of patients treated with arthrotomy and primary repair. *Am J Sports Med* 2009;37:65-71.
14. Grontvedt T, Engebretsen L, Benum P, Fasting O, Molster A, Strand T. A prospective, randomized study of three operations for acute rupture of the anterior cruciate ligament. Five-year follow-up of one hundred and thirty-one patients. *J Bone Joint Surg Am* 1996;78:159-168.
15. Meunier A, Odensten M, Good L. Long-term results after primary repair or non-surgical treatment of anterior cruciate ligament rupture: A randomized study with a 15-year follow-up. *Scand J Med Sci Sports* 2007;17:230-237.
16. Arbes S, Resinger C, Vecsei V, Nau T. The functional outcome of total tears of the anterior cruciate ligament (ACL) in the skeletally immature patient. *Int Orthop* 2007;31:471-475.
17. Toy JO, Feeley BT, Gulotta LV, Warren RF. Arthroscopic avulsion repair of a pediatric ACL with an anomalous primary insertion into the lateral meniscus. *HSS J* 2011;7:190-193.
18. Gaulrapp HM, Haus J. Intraarticular stabilization after anterior cruciate ligament tear in children and adolescents: Results 6 years after surgery. *Knee Surg Sports Traumatol Arthrosc* 2006;14:417-424.
19. Ahn JH, Han KY, Yu IS, Koh KH. Arthroscopic treatment for tibial "peel off" tears in anterior cruciate ligament-case report. *Eur J Orthop Surg Traumatol* 2013;23:S251-S255 (suppl 2).
20. Seitz H, Menth-Chiari WA, Lang S, Nau T. Histological evaluation of the healing potential of the anterior cruciate ligament by means of augmented and non-augmented repair: An in vivo animal study. *Knee Surg Sports Traumatol Arthrosc* 2008;16:1087-1093.
21. Fisher MB, Jung HJ, McMahon PJ, Woo SL. Evaluation of bone tunnel placement for suture augmentation of an injured anterior cruciate ligament: Effects on joint stability in a goat model. *J Orthop Res* 2010;28:1373-1379.
22. Fisher MB, Jung HJ, McMahon PJ, Woo SL. Suture augmentation following ACL injury to restore the function of the ACL, MCL, and medial meniscus in the goat stifle joint. *J Biomech* 2011;44:1530-1535.
23. Murray MM, Magarian E, Zurakowski D, Fleming BC. Bone-to-bone fixation enhances functional healing of the porcine anterior cruciate ligament using a collagen-platelet composite. *Arthroscopy* 2010;26:S49-S57. suppl.
24. Seitz H, Pichl W, Matzi V, Nau T. Biomechanical evaluation of augmented and nonaugmented primary repair of the anterior cruciate ligament: An in vivo animal study. *Int Orthop* 2013;37:2305-2311.
25. Fleming BC, Magarian EM, Harrison SL, Paller DJ, Murray MM. Collagen scaffold supplementation does not improve the functional properties of the repaired anterior cruciate ligament. *J Orthop Res* 2010;28:703-709.
26. Joshi SM, Mastrangelo AN, Magarian EM, Fleming BC, Murray MM. Collagen-platelet composite enhances biomechanical and histologic healing of the porcine anterior cruciate ligament. *Am J Sports Med* 2009;37:2401-2410.
27. Fisher MB, Liang R, Jung HJ, et al. Potential of healing a transected anterior cruciate ligament with genetically modified extracellular matrix bioscaffolds in a goat model. *Knee Surg Sports Traumatol Arthrosc* 2012;20:1357-1365.
28. Palmer MP, Abreu EL, Mastrangelo A, Murray MM. Injection temperature significantly affects in vitro and in vivo performance of collagen-platelet scaffolds. *J Orthop Res* 2009;27:964-971.
29. Magarian EM, Vavken P, Connolly SA, Mastrangelo AN, Murray MM. Safety of intra-articular use of atelocollagen for enhanced tissue repair. *Open Orthop J* 2012;6:231-238.
30. Murray MM, Spindler KP, Devin C, et al. Use of a collagen-platelet rich plasma scaffold to stimulate healing

of a central defect in the canine ACL. *J Orthop Res* 2006;24:820-830.
31. Murray MM, Spindler KP, Abreu E, et al. Collagen-platelet rich plasma hydrogel enhances primary repair of the porcine anterior cruciate ligament. *J Orthop Res* 2007;25:81-91.
32. Murray MM, Palmer M, Abreu E, Spindler KP, Zurakowski D, Fleming BC. Platelet-rich plasma alone is not sufficient to enhance suture repair of the ACL in skeletally immature animals: An in vivo study. *J Orthop Res* 2009;27:639-645.
33. Mastrangelo AN, Vavken P, Fleming BC, Harrison SL, Murray MM. Reduced platelet concentration does not harm PRP effectiveness for ACL repair in a porcine in vivo model. *J Orthop Res* 2011;29:1002-1007.
34. Murray MM, Magarian EM, Harrison SL, Mastrangelo AN, Zurakowski D, Fleming BC. The effect of skeletal maturity on functional healing of the anterior cruciate ligament. *J Bone Joint Surg Am* 2010;92:2039-2049.
35. Vavken P, Saad FA, Fleming BC, Murray MM. VEGF receptor mRNA expression by ACL fibroblasts is associated with functional healing of the ACL. *Knee Surg Sports Traumatol Arthrosc* 2011;19:1675-1682.
36. Haus BM, Mastrangelo AN, Murray MM. Effect of anterior cruciate healing on the uninjured ligament insertion site. *J Orthop Res* 2012;30:86-94.
37. Magarian EM, Fleming BC, Harrison SL, Mastrangelo AN, Badger GJ, Murray MM. Delay of 2 or 6 weeks adversely affects the functional outcome of augmented primary repair of the porcine anterior cruciate ligament. *Am J Sports Med* 2010;38:2528-2534.
38. Vavken P, Fleming BC, Mastrangelo AN, Machan JT, Murray MM. Biomechanical outcomes after bioenhanced anterior cruciate ligament repair and anterior cruciate ligament reconstruction are equal in a porcine model. *Arthroscopy* 2012;28:672-680.
39. Murray MM, Fleming BC. Use of a bioactive scaffold to stimulate anterior cruciate ligament healing also minimizes posttraumatic osteoarthritis after surgery. *Am J Sports Med* 2013;41:1762-1770.
40. Sherman MF, Lieber L, Bonamo JR, Podesta L, Reiter I. The long-term followup of primary anterior cruciate ligament repair. Defining a rationale for augmentation. *Am J Sports Med* 1991;19:243-255.
41. Wasmaier J, Kubik-Huch R, Pfirrmann C, Grehn H, Bieg C, Eid K. Proximal anterior cruciate ligament tears: The healing response technique versus conservative treatment. *J Knee Surg* 2013;26:263-271.
42. Steadman JR, Cameron-Donaldson ML, Briggs KK, Rodkey WG. A minimally invasive technique ("healing response") to treat proximal ACL injuries in skeletally immature athletes. *J Knee Surg* 2006;19:8-13.
43. Nguyen DT, Geel J, Schultze M, et al. Healing of the goat anterior cruciate ligament after a new suture repair technique and bioscaffold treatment. *Tissue Eng Part A* 2013;19:2292-2299.