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Review Article

The non-reconstructive treatment of complete ACL tear with biological enhancement in clinical and preclinical studies: A systematic review

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A B S T R A C T

Introduction: There is still controversy regarding the bio-enhanced non-reconstructive ACL treatment.
Materials and methods: A search for articles in databases was performed in February 2017. The objective and subjective evaluations of clinical studies and biomechanical and histological data of preclinical studies were extracted.
Results: Eighteen articles were included for analysis. In clinical studies, although subjective scores were significantly improved, the rate of re-operation rate was high. In preclinical studies, bio-enhancing techniques demonstrated promotion of the healing of ACL.
Conclusions: The efficacy of biological enhancement cannot be validated in clinical studies. Preclinical studies showed improved biomechanical and healing potential.

Contents

Introduction

Currently, anterior cruciate ligament (ACL) reconstruction has been considered as the primary treatment of active young adult patients with ACL complete tear. However, there is still controversy

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regarding the best treatment algorithm of ACL tear in adolescent,[1–4] the middle-aged to elderly,[5,6] skeletally immature and low-demanding adult patients. In addition, tendon-bone healing,[7] donor site morbidity,[8] destruction of proprioception and vascularity, and non-anatomic placement were all potential problems for reconstructive treatment. Non-reconstructive approach primarily avoids the use of graft and extra trauma caused by drilling bone tunnels, and probably preserves more proprioception with less destruction of ACL footprint.

Theoretically, torn ACL has healing potential.[9] However, the outcome of non-reconstructive ACL treatment was not promising. In a long-term follow-up study, Sanders et al.[10] demonstrated 18-fold likelihood of secondary meniscal tears, 14-fold of arthritis, and 5-fold of need of total knee arthroplasty with non-reconstructive treatment comparing with ACLR. Similarly, discouraging outcome of ACL single repair was also reported by a recent systematic review.[3] From the above discouraging results, it seems that the self-healing capacity of ACL is very low, biological enhancement of healing may be necessary to keep the advantages of non-reconstructive surgery and ensure sufficient healing responses and good clinical outcomes.

The biological enhancement technique in ACL reconstruction has been well discussed in a systematic review by Fu et al.[11] They suggested that biological modulation is able to promote healing at the tunnel-graft interface. But the healing of the intra-articular midsubstance of the graft was another consideration. We included clinical and extended to preclinical studies that may provide more advanced insight for the further ACL tear treatment. In the literature, “Healing Response Technique” (HRT) and “Dynamic Intraligamentous Stabilization” (DIS) are two mainly used techniques in clinical studies, while a variety of innovative techniques were also applied in animal studies. HRT was described as perforating cortical bone at the femoral origin and the rupture stump, while DIS is employing internal stabilizer to keep the unstable knee in a posterior translation, combined with microfracturing and platelet-rich fibrin induction at the rupture site to promote self-healing.

The purpose of the systematic review was to describe the clinical outcome and results of animal studies on non-reconstructive treatment of complete anterior cruciate ligament (ACL) tear with biological enhancement.

Materials and methods

We searched the Medline, Scopus and Ovid database in January 2018 to identify all clinical and preclinical studies about the treatment of complete ACL tear with non-reconstructive biological enhancement techniques based on the following criteria: (ACL OR anterior cruciate ligament) AND (repair OR healing) NOT (reconstruct*). The references of all included studies and related reviews were also checked. The inclusion criteria were (1) English original articles published from January 1, 2000 to January 20, 2018; (2) clinical or animal in vivo studies; (3) complete ACL tear; (4) and healing of ACL was enhanced by the use of bone marrow stimulation, mesenchymal stem cells, growth factors, biomaterials, drugs or biophysical intervention (biological enhancement). Articles were excluded if they (1) were reviews, meta-analyses, case reports, or technical notes; (2) had application of any type of graft; (3) included concomitant posterior cruciate ligament and posterolateral complex lesions and patellofemoral disorders. It should be noted that since the management for ACL partial tear is different from complete tear and the relevant articles of partial tear was too few to synthesize, articles about partial tear were also excluded. All included studies retrieved from the search engines were initially checked manually by 2 independent co-authors by reviewing titles, abstracts and full-text articles for final application of the inclusion and exclusion criteria. Any discrepancies were discussed and overcome by consensus.

The full texts of the filtered included articles were then obtained for data extraction. Data from clinical studies were mainly publication years, first author, type of biological enhancement and combined surgery, sample size, patients' demographic data, key objective and subjective outcome measures, and other major findings. Data from animal studies were mainly publication years, first author, type of biological enhancement and combined surgery, animal model, sample size, grouping methods, time of sacrifice, histological or radiological results, laxity data, and biomechanical data.

Assessment of quality of clinical studies and animal studies was then performed by two experienced clinicians and two senior researchers, respectively. Clinical studies were assessed with methodological index for non-randomized studies (MINORS).[12] Since there were four additional criteria for comparative study, the ideal score was 16 for non-comparative studies and 24 for comparative studies. Animal studies were assessed according to the criteria adapted from the checklist of Hooijmans et al.[13] The average score of the two reviewers were recorded as the final score.

Results

The initial research resulted in 1023 articles. After the filtered research, 508 articles were excluded for publication date, type and language. The review on titles was conducted on 515 articles. After the exclusion of 380 irrelevant articles, 135 articles were available for further screening. Twenty-two eligible articles were retrieved. It should be noted that the article written by Eggli et al., in 2015[14] included the same series as they published in 2016[15], so the earlier article was not included for analysis. So 18 articles were finally included for analysis. Among them, seven articles were clinical studies and 11 articles were animal studies. Of the 7 clinical studies, there were 5 level IV case-series studies,[2,15–18] 1 level III retrospective case-control studies[19] and 1 level III cohort study[20] (Fig. 1). There were three techniques discussed in all 7 articles, HRT in 3 studies, DIS repair in 3 studies and bridge-enhanced ACL repair. One of the level III studies compared the outcome of DIS repair with and without additional collagen application.[19] The other one compared the HRT and conservative treatment.[17] Of the 11 animal studies, six compared bio-enhanced ACL repair and suture repair only,[1,21–26] one compared bio-enhanced repair with ACL reconstruction,[27] and compared the outcome of bio-enhanced ACL repair with different fixation methods,[28] platelet-rich plasma (PRP) injection temperature,[29] concentration of PRP[30] and time of delay.[31]

Methodological quality assessment

For clinical studies, there were 4 cases-series studies, 2 case-control and 1 cohort studies. The quality scores were listed in the last column of Table 1. According to MINORS scoring system, comparative studies was evaluated by 4 more items than case-series studies. For animal studies, eight of twelve studies scores 5–8, while 4 studies scored lower than 5, and they were considered as low-quality studies. Good interobserver reliability was obtained between assessors (intraclass correlation coefficient, 0.882; animal studies, intraclass correlation coefficient, 0.807), and consensus on scoring was reached by discussion.

Clinical studies

In total, 193 knees (129 male, 64 female) were evaluated at a

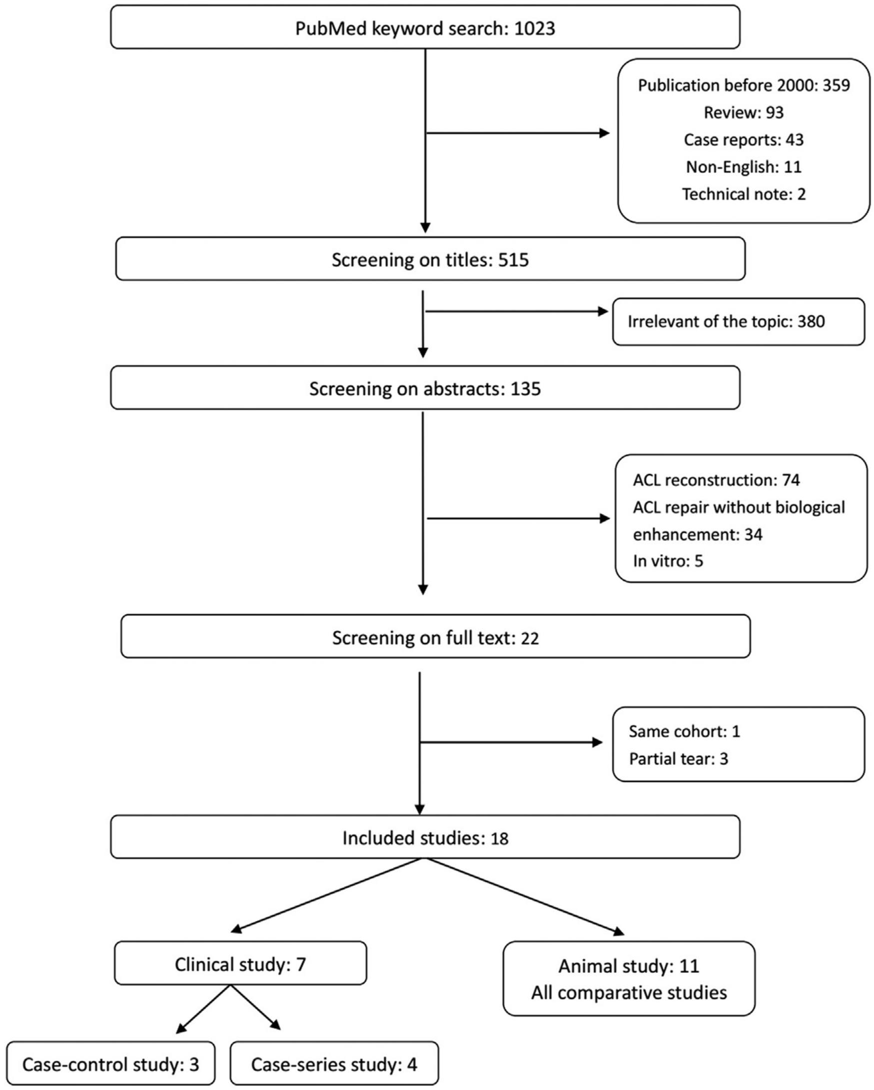

Fig. 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart.

minimum follow-up of 2 years. Of all 193 knees, 91 knees (47.2%) were treated with HRT which is fundamentally microfracture at the femoral insertion site without suturing ACL, 102 knees (52.8%) were treated with DIS repair with biological enhancement technique, and 10 knees were treated with bridge-enhance ACL repair procedure (BEAR) (Table 1).

All studies reported the Lysholm and Tegner score at the final follow-up. For HRT studies, the median or mean Lysholm scores ranged from 90 to 96 scores. The median or mean Tegner scores ranged from 5 to 8.5 scores, and failure rate from 8.9% to 36%. For DIS studies, the median or mean Lysholm scores ranged from 97 to 100 scores. The median or mean Tegner scores ranged from 5.1 to 6 scores, and failure rate from 0% to 20%. The BEAR scaffold in Murray et al.'s clinical study[20] is the only device that fills the gap between the torn ligament ends to have current Investigational Device Exemption approval from the Food and Drug Administration. At 3-month follow-up, no joint infections or signs of significant inflammation were observed. There were no differences between groups in effusion or pain, and no failures by Lachman examination criteria or MRI evaluation.

Animal studies

There were 11 eligible animal studies included for quantitative synthesis (Table 2). Among them, there were 8 studies on pigs, 1 on minipigs and 2 on goats. The biological enhancement was mainly focused on 4 techniques: bio-enhanced ACL repair with collagen-platelet composite (CPC) combined with bone marrow stimulation or other biomaterials,[27] suture repair enhanced by PRP, locking suture technique with small intestinal submucosa (SIS) and suture repair wrapped by extracellular matrix (ECM) bioscaffolds and injected with ECM hydrogel.[25]

Collagen-platelet composite

In the 7 studies[21,22,27–31] focusing on the application of CPC. Among them, three of four studies[21,22,27,28] that made direct comparison between bio-enhanced repair and repair only favored the bio-enhanced ACL repair. Vavken et al.[27] proved that bio-enhanced ACL repair produced similar anterior-posterior (AP) laxity at 30°, 60°and 90°, maximum load, maximum displacement and linear stiffness with ACLR in a skeletally immature, large animal model.

Table 1
Summary of clinical studies.

Study	Study design	Patients included	M:F	Average age, yr	Mean F/U, mo	Bio-enhancement techniques	Surgical procedure on ACL	Rate of reoperation	Assessment of outcome	MINORS
Steadman et al.[2]	Case series	13	9:4	13	69	Bone marrow stimulation	ACL perforation	23.1%	Instrumented SSD: 5 (3–10)mm Lysholm: 96, Tegner: 8.5	11
Steadman et al.[16]	Case series	48	13:35	51	91.2	Bone marrow stimulation	ACL perforation	8.9%	More than 90% lower than Lachman Grade 3 Lysholm: 90, Tegner: 5	10
Wasmaier et al.[17]	Case series	28	20:10	30.5	51.0	Bone marrow stimulation	ACL perforation	36%	Significant higher anterior knee laxity Lysholm: 91.2, Tegner: 5.7	16
Evangelopoulos et al.[19]	Case control	Study: 23 Control: 33	39:17	30	24	Collagen membrane	DIS repair	0%	Study group vs control group Instrumented SSD: 1.0 mm vs 1.0 mm Lysholm: 100 vs 95 Tegner: 6 vs 5	19
Henle et al.[18,a]	Case series	69	42:27	32.4	≥24	Microfracturing	Sutures and DIS	2.9%	Instrumented SSD: 2.3 mm Lysholm: 97, Tegner: 5.1, IKDC: 94.8	10
Eggli et al.[15]	Case series	10	8:2	23.3	60.3	Microfracturing	Sutures and DIS	20%	Instrumented SSD: 2 mm Lysholm: 100, Tegner: 5.5, IKDC: 98.9	10
Murray et al.[20]	Cohort	Study: 10 Control: 10	6:14	24	3	BEAR scaffold	Suture	0%	Study group vs control group Lachman test: 8 grade A, 2 grade B vs 10 grade A IKDC: 54.3 vs 60.7	20

M, male; F, female; mo, months; yr, year; F/U, follow-up; d, day; mo, month NP, not provided; HRT, healing response technique; DIS, dynamic intraligamentary stabilization.
[a] There were 278 patients included in this study but only 69 patients were followed for a minimum of 2 years. The M:F, age at surgery, time from injury to surgery were obtained from the overall data.

Table 2
Summary of animal studies.

Study	Animals	Study design	F/U	Outcome
Vavken et al.[14]	24 pigs	CPC vs ACLR vs control	15 wk	CPC and ACLR produced superior biomechanical outcomes to control group.
Kiapour et al.[18]	17 pigs	CPC vs control	15 wk	CPC showed worse mechanical outcome than control group
Murray et al.[23]	12 pigs	CPC with ligament fixation vs tibial fixation	15 wk	Tibial fixation significantly improved mechanical outcomes.
Joshi et al.[19]	27 pigs	CPC vs control	4 wk 6 wk 3 mo	CPC showed in improvements in mechanical and histological assessments at 3 months.
Murray et al.[20]	5 pigs	Hydrogel-PRP vs control	4 wk	Hydrogel-PRP showed improvements in mechanical assessments.
Magarian et al.[26]	16 pigs	CPC immediate repair vs delay of 2wks vs 6wks	15 wk	Delay of 2wks and 6wks both showed inferior mechanical outcomes and laxity test results.
Nguyen et al.[21]	10 goats	Locking suture technique with and without SIS vs intact control	12 wk	The cross-sectional area of two suture groups was 35% and 50% of the intact control, respectively. Suture-SIS group showed mechanical improvement than the Suture group at 30°.
Palmer et al.[24]	4 pigs	CPC repair at 28.9–32.4 °C	14 wk	The mechanical property and histological outcome were inversely correlated with injection temperature.
Fisher et al.[22]	16 goats	ECM sheet and hydrogel vs control	12 wk	The cross-sectional area and mechanical outcomes of ECM study group were significant better than control.
Murray et al.[1]	6 pigs	PRP vs control	14 wk	No significant mechanical improvement in PRP group
Mastrangelo et al.[25]	8 minipigs	Two groups: CPC with PRP 5x vs 3x baseline of platelets	13 wk	5x baseline concentration resulted in a decrease in histological outcome.

ACL, anterior cruciate ligament; CPC, collagen platelet composite; F/U, follow up; wk, week; mo, month; PRP, platelet-rich plasma; AP, anterior-posterior; SIS, small intestinal submucosa; ECM, extra-cellular matrix.

Joshi et al.[22] discovered the technique produced the CPC ligaments a 76% greater yield at load, a 320% increase in linear stiffness, and a 47% decrease in the displacement at yield comparing with suture repair only after 3 months of healing. Histologically, although the CPC group had a significantly higher proportion of fusiform cells at the 3-month time point than suture only group, there were still significant difference in cellularity, cell shape, vascularity, and collagen organization from intact ligament. Murray et al.[28] modified the fixation to a bone-to-bone fashion and proved its enhancement of yield load and linear stiffness comparing with bone-to-ligament fixation. However, the AP laxity of both techniques was still significantly greater than the intact knee.

On the contrary, Kiapour[21] discovered that when treated with absorbable suture, females had a lower ACL linear stiffness, yield load, maximum load and AP stability at 30° than suture repair only.

The condition of CPC application was also discussed. Magarian[32] reported that after a delay of 2 or 6 weeks between transection and repair, the yield load of at postoperative 15 weeks was decreased by 40% and 60%, maximum load decreased 55% and 60%, linear stiffness decreased 50% and 50%, and AP laxity was 40% and 10% higher, respectively. Mastrangelo[30] reduced the concentration of PRP within the CPC from 5 times of systemic baseline to 3 times. There was no significant deterioration in biomechanical properties or AP laxity at 30ºand 90°, but significant greater laxity at 60°, and worse histological characteristics (cellular density, orientation, shape, collagen formation and maturity index). Palmer[29] conducted a research on the effect of application temperature of CPC on the ligament. In the in vitro study, injection temperatures of over 30 °C resulted in gels with 50% lower stiffness than those below 30 °C. In the in vivo study, CPCs injected at a higher temperature resulted in 50% of the repair strength when the temperature increased from 29 °C to 32.5 °C.

Suture repair and platelet-rich plasma

Two studies reported the results after PRP application. Murray et al. [23]injected hydrogel-PRP to the repair site enhance the suture repair. In the comparison with suture only, the bio-enhanced repair acquired 164%, 123% and 110% increase for load at yield, maximum load and tangent modulus, respectively, although the above parameters were still inferior to intact knee. However, in another study by Murray et al.,[1] they concluded that PRP alone was not sufficient to enhance ACL suture repair in terms of AP laxity and biomechanical properties.

Suture repair and small intestinal submucosa

In the study by Nguyen et al.,[24] ACLs were sutured with customized-Becker suture technique. Goats were divided into two groups, suture only group and suture + SIS group in which six small pieces of SIS (2 mm*2 mm*200 μm) were placed within the mid-substance of the injury site. After 12 weeks of healing, the AP laxity at 30°, 60ºand 90° was significantly greater in both groups than control. Gross morphology showed that the healing ACL was continuous with collagenous tissue in both groups. The cross-sectional area of the Suture and the Suture + SIS group was 35% and50% of the intact control, respectively.

Extracellular matrix sheet and gel

In the research by Fisher et al.,[25] sixteen skeletally mature ACL-transected goats were divided into two groups, the ECM-treated group in which an ECM sheet was wrapped around the injury site and with an ECM hydrogel injected into the transected site and the suture repair group in which the ACL was repaired by suture only. It demonstrated that the AP laxity of the ECM treated group was significantly greater than the sham control. Histologically, all ECM-treated ACLs healed with continuous neo-tissue formation and no noticeable concavities while only a small amount of neo-tissue formation in the suture repair group. The cross-sectional area of the ECM-treated group was similar to sham operated controls and was 4.5 times those of suture repair group. Biomechanically, stiffness and ultimate load for the ECM-treated reached 48% and 20% of the sham control. They concluded that the application of an ECM bio-scaffold and hydrogel was found to accelerate the healing of a transected ACL following suture repair but failed to fully restore the function of normal ACL.

Discussion

The most important finding of the systematic review was (1) improved biomechanical and healing potential in bio-enhanced ACL non-reconstructive treatment, (2) the satisfactory subjective outcome but an unacceptable high rate of re-instability and reoperation, especially for some studies with HRT, although the validity of the findings were limited by low level of evidence.

In a systematic review of primary ACL repair, 20%–64% of patients underwent revision for re-instability.[3,33] In a 32-year follow-up study by Taylor et al.,[34] 28% of patients ultimately underwent an additional procedure for persistent symptomatic instability. Similarly, in the study by Strand et al.,[35] at a 15–23-year follow-up, the rate of instability was as high as 43%. Since the discouraging clinical outcome of ACL single repair,[3,35] ACLR has become a popular treatment of ACL rupture. However, comparing with non-reconstructive treatment, ACLR was not advantageous in skeletally immature, adolescent,[36] elder and non-active patients. In addition, the bone-tendon healing,[7] donor site morbidity,[8] non-anatomic placement were also potential problems. If ACL repair can be successfully achieved, several advantages can be further provided, including the preservation of natural anatomy (femoral and tibial insertion sites and multi-bundle nature), proprioception, and vascularity.[37]

Unfortunately, unlike extra-articular ligament like medial collateral ligament (MCL) which can successfully heal within blood clot formation, the healing potential of ACL was compromised by the abundance of plasmin in synovial fluid which is an efficient cleaver of fibrin clot.[38] In addition to the hostile environment, ACL healing can also be compromised by biological factors such as cell deficiencies and alterations in cellular metabolism.[14] Given the poor healing capability of nature ACL, several biological enhancement techniques for ACL healing have been proposed. So the goal of this systematic review was to synthesize the results of preclinical and clinical studies respectively.

All included animal studies were comparative studies. Of the 11 animal studies, six compared bio-enhance ACL repair and suture repair only[1,21–25,28] and one compared bio-enhanced repair with ACL reconstruction. The results were still controversial. Two studies reported discouraging results. Murray et al.[1] found that PRP only was not sufficient to enhance ACL healing. Kiapour et al.[21] demonstrated inferior linear stiffness, ACL yield, maximum load, and AP stability in female subjects with bio-enhanced repair than non-absorbable suture repair. However, the other four studies support that bio-enhancement technique did improve at least some of the biomechanical or laxity properties. In a comparison with ACL reconstruction, Vavken et al.[27] showed that bio-enhanced ACL repair produced similar biomechanical results with ACL reconstruction in a skeletally immature porcine model. If we categorized the studies into different approaches of enhancement, the CPC was most discussed and favored by most studies.

In terms of clinical studies, the rates of re-instability were 8.9%, 23.1% and 36% in HRT studies, and 0%, 4.0% and 20% in DIS studies. In terms of the re-operation rates, for HRT they were 8.9%, 23.1% and 36%, while for DIS, they were 0%, 2.9% and 10%. It should be noted that, Steadman et al. reported the rate of 8.9% in an older and less active population (mean age: 51, final Tegner score: 5) than Wasmaier et al.'s cases (mean age: 31, final Tegner score: 5.7) whose re-operation rate was 36%. It seems that the DIS technique acquired relatively lower rate of re-instability and re-operation.

According to literature, there are two main factors that influence the wound healing, mechanical and biological environment.[39] In terms of the mechanical environment, the major difference between these two techniques was the structural continuity provided by intraligamentous stabilizer. DIS acted as an internal brace that provided torn ACL a stable mechanical environment for healing. Although patients were locked in full extension with weight-bearing for a total of 6 weeks and the ACL stump was held by marrow clots, the anterior tibial translation and micro-movement in synovial fluid might be inevitable.

On the other hand, in terms of biological environment, in addition to microfracture, Eggli et al.[15] also introduced leukocyte- and platelet-rich fibrin, and Evangelopoulos et al.[19] applied collagen scaffold with DIS technique which could also be a reason of better outcome. The only study comparing ACL repair and ACLR was an early feasibility cohort study which was only followed for 3 months.[40] The percent recovery of hamstring strength was greater at 3 months for the bio-enhanced group. No significant difference was detected in terms of adverse events, objective and subjective assessments and MRI (magnetic resonance imaging) findings.

The only study that had been translated from preclinical to clinical application was performed by Murray et al.[20] The effectiveness of BEAR scaffold which was the only device that fills the gap between the torn ligament ends to have current Investigational Device Exemption approval from the Food and Drug Administration has been proved by some of the preclinical studies that included in our review.[22,26,41] In Murray et al.'s early pilot clinical study,[20] no significant adverse event or no difference in terms of effusion or pain or objective evaluations were observed in the 10 patients treated with BEAR procedure, although the follow-up was only 3 month. Providing ACL a stable mechanical environment for healing and an enhanced biological environment, and verified by preclinical studies, the long-term validity of BEAR procedure is promising.

This study is mainly focused on ACL complete tear, however, a glimpse at the results of biological enhancement of partial tear healing may be inspiring. Although the evidence was limited, the outcome of biological enhancement in the treatment of ACL partial tear seemed promising. Gobbi et al.[42] treated incomplete proximal ACL tears with single repair and bone marrow stimulation. At a mean of 25.3 months (range, 17–38 months) follow-up, the SSD reduced from 3.5 mm to 1.3 mm. Tegner, Marx and Noyes score significantly improved and restored to a similar level as pre-injury. Seijas et al.[43] applied PRGF-Endoret in the remaining intact bundle for football players. Fourteen of 19 patients returned to their pre-injury sports level 9 or 10 at 2-year follow-up. Murray et al.[23] demonstrated significant effects on the composition of tissue filling the wound, increasing the presence of some cytokines to a similar level of that observed in the extra-articular ligament after the application of collagen-PRP hydrogel on an ACL central-wound model. It should be noted that although the results seems promising, partial tear of the ACL needs more extensive work and discussion in near future with more evidence.

The preservation of proprioception was considered a main advantage of ACL repair. Henle et al.[18] attributed their excellent clinical outcome to the preservation of proprioception. However, none of the 7 included clinical studies or studies on partial tear conducted any assessment on proprioception. Although it's not the same grade of preservation, remnant preserving in ACLR might also provide some information. In a study by Hong et al.,[44] the passive angle reproduction test result at 15° was $3.6^\circ \pm 1.8^\circ$ in the remnant preserving group and $3.9^\circ \pm 2.2^\circ$ in the standard ACLR group ($P = 0.739$). In contrast, in another study,[45] the final accuracy of joint position sense of remnant preserving group was significantly better than standard ACLR ($0.7 \pm 0.7^\circ$ vs. $1.7 \pm 1.2^\circ$, $p < 0.05$).

The timing of ACL repairing was also discussed. Magarian et al.[31] compared the biomechanical properties of ACL repair at time zero, a delay of 2 weeks and 6 weeks. It demonstrated that the yield load decreased by 40% and 60%, maximum load by 55% and 60%, and linear stiffness by 50% and 50% in the group of 2-week and 6-week delay, respectively. AP laxity was 40% higher after 2-week delay and 10% higher after 6-week delay. In the present review of clinical studies, surgeries were performed within a mean of 18 days from initial injury. And all animal studies performed repair at time zero. So it seemed that the ruptured ACL should be repaired in acute phase.

There were some limitations in the present study. First, we classified marrow stimulation as a bio-enhancement approach, but the component of blood clot was different from traditional blood-derived bio-enhancement approach, like PRP. PRP is a concentrated source of platelet and contains a large amount of native growth factors without erythrocytes that would be expected to undergo necrosis shortly after clot formation,[46] while blood clot contains all components of full blood without concentration. Second, there is a chance that we may miss some relevant study because of publication bias and some gray literature. Third, only 2 of 6 clinical studies were retrospective comparative studies and the level of evidence was not higher than three. Fourth, the bio-enhancement technique was not homogeneous for both clinical and animal studies, although we illustrated the results according to different techniques. Fifth, some animal studies of the bio-enhanced ACL repair and suture repair are from the same research group, so the results may be biased. Last, the results of animal studies cannot be directly interpreted to human outcomes.

Conclusion

The efficacy of biological enhancement cannot be validated because of the low level of evidence of included studies. Animal studies showed improved biomechanical and healing potential in bio-enhanced ACL non-reconstructive treatment.

Conflicts of interest

The authors have declared no financial conflicts of interest with respect to their authorship and publication of this work.

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