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# Scaffolds for tendon and ligament repair: review of the efficacy of commercial products

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Jimin Chen, Jiake Xu,  
Allan Wang and  
Minghao Zheng<sup>†</sup>

<sup>†</sup>Author for correspondence  
Centre for Orthopaedics  
Research, School of Surgery  
University of Western Australia,  
Room 2.33, 2nd Floor, M-Block,  
QEll Medical Centre, Nedlands,  
Perth, WA 6009, Australia  
Tel.: +61 893 463 213  
Fax: +61 893 463 210  
[minghao.zheng@uwa.edu.au](mailto:minghao.zheng@uwa.edu.au)

Driven by market demand, many biological and synthetic scaffolds have been developed during the last 15 years. Both positive and negative results have been reported in clinical applications for tendon and ligament repair. To obtain data for this review, multiple electronic databases were used (e.g., Pubmed and ScienceDirect), as well as the US FDA website and the reference lists from clinical trials, review articles and company reports, in order to identify studies relating to the use of these commercial scaffolds for tendon and ligament repair. The commercial names of each scaffold and the keywords 'tendon' and 'ligament' were used as the search terms. Initially, 378 articles were identified. Of these, 47 were clinical studies and the others were reviews, editorials, commentaries, animal studies or related to applications other than tendons and ligaments. The outcomes were reviewed in 47 reports (six on Restore™, eight on Graftjacket®, four on Zimmer®, one on TissueMend®, five on Gore-Tex®, six on Lars®, 18 on Leeds–Keio® and one study used both Restore and Graftjacket). The advantages, disadvantages and future perspectives regarding the use of commercial scaffolds for tendon and ligament treatment are discussed. Both biological and synthetic scaffolds can cause adverse events such as noninfectious effusion and synovitis, which result in the failure of surgery. Future improvements should focus on both mechanical properties and biocompatibility. Nanoscaffold manufactured using electrospinning technology may provide great improvement in future practice.

**KEYWORDS:** biological scaffold • commercial scaffold • ligament • repair • synthetic scaffold • tendon

Tendon and ligament injuries are among the most common health problem affecting the adult population. The rotator cuff, extensor carpi radialis brevis (tennis elbow), anterior cruciate ligament (ACL) and Achilles tendon are all susceptible to occupational or sporting injuries. It has been reported that 13% of individuals aged 50–59 years and 51% of people over the age of 80 years experience rotator cuff injury, with over 50,000 patients requiring surgical repair in the USA each year [1,2]. In addition, 11% of regular runners suffer from Achilles tendinopathy [3]. In the USA, there are 75,000 cases of ACL rupture [4] and 5 million new cases of tennis elbow [5] reported each year. The prevalence of such injuries means that the cost of treating tendon and ligament injury has placed a huge burden on the healthcare system worldwide. In Australia, direct medical expense for rotator cuff repair is estimated to be 250 million annually.

In 2000, treatments for shoulder pain cost the US government up to \$7 billion [6] and the total cost for tendon and ligament injury has been estimated at \$30 billion annually. Clearly, tendon and ligament injury dramatically affects the quality of life of patients and adds financial pressure to the economy.

Surgical treatment is usually reserved for patients who fail to improve after a period of conservative treatment. Tendon graft, either autografts, allografts or xenografts, may be needed in cases where the tendon defect is so large that it can not be repaired by the native tissue. While the use of autograft tissue is frequently limited by availability and donor site complication, allografts and xenografts have become increasingly popular for tendon and ligament repair. Driven by market demand, many biological and synthetic scaffolds have been developed during the last 15 years. The most popular

commercial scaffolds include GraftJacket® (Wright Medical, TN, USA), Restore™ (DePuy Orthopedics, IN, USA), TissueMend® (Stryker Orthopedics, NJ, USA), CuffPatch® (Arthrotek, IN, USA), Zimmer patch formerly known as Permacol™ (Zimmer, IN, USA), Shelhigh No-React® Encuff Patch (Shelhigh Inc., NJ, USA), OrthADAPT® (Pegasus Biologic Inc., CA, USA), Bio-Blanket® (Kensey Nash Corp., PA, USA), Gore-Tex® patch WL (Gore and Associates, Flagstaff, AZ, USA), Lars® ligament (Dijon, France), Leeds-Keio® or Poly-tape® (Xiros plc, Neoligaments, Leeds, UK; Yufu Itonaga Co., Ltd Tokyo Japan) and Artelon® & Sportmesh™ (Artimplant AB, Sweden & Biomet Sports Medicine, IN, USA).

This review investigates the efficacy of current commercial scaffolds for tendon and ligament repair. We have searched multiple electronic databases (e.g., Pubmed and ScienceDirect), as well as the US FDA websites and reference lists in clinical trials, review articles and company reports, in order to identify studies relevant to the use of these commercial scaffolds for tendon and ligament repair. The keywords 'tendon' and 'ligament', and the commercial names of each scaffold were used as the search terms. A total of 378 articles were identified initially. Of these, 47 were clinical studies and the others were reviews, editorials, commentaries or animal studies, or related to subjects other than tendon and ligament repair. Outcomes of scaffolds were reviewed in the 47 clinical reports, of which there were six on Restore, eight on GraftJacket, four on Zimmer, one on TissueMend, five on Gore-Tex, six on Lars, 18 on Leeds-Keio, and one study used both Restore and GraftJacket. No clinical studies using Shelhigh No-React Encuff Patch, OrthADAPT, Bio-Blanket and Artelon & Sportmesh for tendon or ligament repair were identified at the time of our search. In total, these 47 reports included 1499 patients of which 225 patients were rotator cuff repair (14 reports), 650 had ACL reconstruction (17 reports), 42 had Achilles surgery (four reports), 451 had ankle lateral ligament reconstruction (one report), 81 had patellar tendon repair (six reports), 26 had lateral collateral ligament reconstruction (one report), 16 had trapeziectomy (one report) and one had iliofemoral ligament reconstruction (one report).

### Biological scaffolds

Biological scaffolds are derived from mammalian tissues, which include human, porcine, bovine and equine sources. Tissue, such as dermis, small intestine submucosa and pericardium, were processed through cascade steps that included general cleaning, removal of lipids or fat deposits, disruption of cellular and DNA materials, cross-linking, and sterilization. The ultimate goal of this process is to remove any noncollagen components that may cause host rejection, while retaining its natural collagen structure and mechanical properties. The end-stage products are composed predominately of naturally occurring collagen fibers, mainly type I collagen. Many scaffolds also possess a surface chemistry and native structure that is bioactive and promotes cellular proliferation and tissue ingrowth. Scaffolds used for tendon and ligament reconstruction that are considered to be biological include Restore, GraftJacket, Zimmer, TissueMend, CuffPatch,

Shelhigh No-React Encuff Patch, OrthADAPT and Bio-Blanket. Information regarding the source and manufacturers of these biological scaffolds was obtained from the FDA and company websites and data is summarized in TABLE 1. The outcomes of clinical studies using these biological scaffolds for tendon or ligament repairing are summarized in the following sections.

The Restore membrane was the first commercially available biological scaffold on the market. It is sourced from the small intestine submucosa of pathogen-free pigs and composed of more than 90% fibrillar collagen (types I, II and V), together with approximately 5–10% lipids, a small amount of carbohydrates and TGF- $\beta$  [7,8]. Several animal studies [7,9] and a clinical investigation [10] have demonstrated the efficacy of Restore in rotator cuff tendon repair but subsequent studies have shown that Restore is not suitable for cuff tendon reconstruction [11–13]. A randomized, controlled trial, which matched the age, sex and tear size of rotator cuff, was conducted by Iannotti to evaluate the efficacy of Restore Patch. The results showed that nine out of 15 Restore recipients had improved patient outcome and six out of 15 control patients failed the surgery within the 14-month follow-up period [13]. Other studies also reported very high failure rates while using Restore for rotator cuff tear. Sclamberg reported that ten out of 11 patients underwent rerupture [14], while Walton reported that six out of ten patients [12] suffer a retear by 6–24 months after the surgery. In short, all of these studies showed that augmentation of rotator cuff tear with the Restore did not improve the rate of tendon healing or clinical outcomes. The major side effect caused by the implantation of Restore patch is severe postoperative edema, which is not related to infection [11–13]. For many years Restore has been marketed as an acellular collagen scaffold containing growth factors [7]. However, we found that Restore is not an acellular matrix and contains porcine DNA, which may cause complications in human use [15]. The noninfectious edema is probably due to immune response to the remaining porcine genetic material. Based on literature, we conclude that Restore or scaffolds sourced from small intestine submucosa are ineffective in the reinforcement of large rotator cuff tears and are currently not recommended for use in cuff tendon repair. Other scaffolds sourced from small intestine submucosa are also readily available on the market. These include Oass™, Surgisis™ (Cook Biotech Inc.) and CuffPatch™ (Organogenesis Inc.). As they were from the same source as Restore, extra care should be taken to monitor the adverse events when applied in patients.

GraftJacket is sourced from cadaver human skin, which undergoes processing to remove the cellular component while preserving the native protein, collagen structure, blood vessel channels and essential biochemical composition [20]. Satisfactory results have been described using GraftJacket for skin lesion [16–18] and abdominal wall repair [19,20]. GraftJacket has also been tested for chronic and acute Achilles tendon rupture [21–24]. In 2004, Lee first reinforced a gastrocnemius turndown flap repair with GraftJacket in a 64-year-old woman who had a chronic Achilles tendon rupture at her right heel [21]. Later, a similar technique was applied to nine chronic and 11 acute Achilles tendon rupture repairs [22,24]. A follow-up of all 20 patients up to 31 months

**Table 1. General information of commercial scaffolds for tendon and ligament repair.**

Brand Name	Texture	Source	Cross-linking	Regulatory approval	Manufacture & distributor	Ref.
Restore™	Biology	Porcine small intestine submucosa	No	US FDA	DePuy Orthopedics, Warsaw, IN, USA	[202]
Graftjacket®	Biology	Human cadaver dermis	No	FDA	Life Cell corporation, Branchburg, NJ, USA Wright Medical, Arlington, TN, USA	[203] [201]
Zimmer® or Permacol™	Biology	Porcine dermis	Yes	FDA	Tissue Science Laboratories, Andover, MA, USA Zimmer, Warsaw, IN, USA	[204] [205]
TissueMend®	Biology	Fetal bovine dermis	Yes	FDA	TEI Biosciences, Boston, MA, USA Stryker Orthopaedics, Mahwah, NJ, USA	[206] [207]
CuffPatch™	Biology	Porcine small intestine submucosa	Yes	FDA	Organogenesis, Canton, MA, USA Arthrotek, Warsaw, IN, USA	[208] [209]
Shelhigh No-React® Encuff Patch	Biology	Bovine or porcine pericardium	Yes	FDA	Shelhigh Inc., NJ, USA	[210]
OrthADAPT™	Biology	Equine pericardium	Yes	FDA	Pegasus Biologic Inc., CA, USA	[211]
Bio-Blanket®	Biology	Bovine dermis	Yes	FDA	Kensey Nash Corp., PA, USA	[212]
Gore-Tex®	Synthetic nonabsorbable	Polytetrafluoroethylene	NA	FDA	WL Gore and Associates, USA	[213]
Lars ligament®	Synthetic nonabsorbable	Terephthalic polyethylene polyester	NA	Canada, Europe	Ligament Augmentation and Reconstruction System, Dijon, France JK Orthomedic Ltd, Quebec, Canada	[214]
Leeds–Keio® or Poly-tape®	Synthetic nonabsorbable	Polyester ethylene terephthalate	NA	Canada, Europe, FDA	Xiros plc, Neoligaments, Leeds, UK Yufu Itonaga Co. Ltd, Tokyo, Japan	[215]
Artelon® and Sportmesh™	Synthetic absorbable	Polyurethane urea polymer	NA	Canada, Europe, FDA	Artimplant AB, Sweden Biomet Sports Medicine, IN, USA	[216] [217]

NA: Not available.  
Information obtained from [218].

postoperatively demonstrated that all were able to perform a single heel raise 6 months after surgery [22,24]. Additionally, two studies have reported the use of GraftJacket to augment massive rotator cuff tear [25–27]. In a small, retrospective series with short-term follow-up of 14.4 months, Burkhead *et al.* reported the improvement of University of California Los Angeles (UCLA) activity level score from 18.4 to 30.4 following surgery [25]. Likewise, Dopirak and Bond reported that augmentation of rotator cuff repair with GraftJacket improved UCLA score from 9.06 to 26.012 at 12 months follow-up [26,27]. However, despite the significant improvement in clinical outcome score, approximately 30% of patients from both studies suffered recurrent tears. Additionally, clinical studies mentioned earlier were retrospective; thus, interpretation of the results is limited by the lack of a proper control. Nevertheless, no adverse events such as inflammatory response, edema or postoperative infection have been reported in studies using GraftJacket for tendon repair. It seems that GraftJacket is

well tolerated by patients. Moreover, GraftJacket has been shown to have the strongest mechanical properties among five popular commercially available scaffolds designed for tendon repair, which may contribute to the repairing process [28].

The Zimmer patch formerly known as Permacol, is considered to be an acellular, cross-linked, collagen-based scaffold sourced from porcine dermal tissue. It is predominately composed of type I collagen (93–95%) together with type III collagen and a small amount of elastin. The Zimmer patch has been used successfully for the reconstruction of human soft connective tissue, such as the abdominal wall, vagina and urinary tract [29–32]. Positive outcomes have been reported in two retrospective studies using the Zimmer patch for rotator cuff reconstruction. Both studies recruited ten patients (five men and five women), and reported great improvement in pain relief, range of motion, satisfaction rate after 1 year of follow-up [33] and constant score improvement from 39.6 to 56.9 [34]. Two patients presented with recurrent tears

in one of the studies [33]. However, both authors supported the use of the Zimmer patch for rotator cuff repair. By contrast, less favorable results have been reported in a study of four patients using a Zimmer patch to bridge rotator cuff defects [35]. Following good postoperative recovery between 3 and 6 months, all four patients showed signs and symptoms of recurrent tear, including aggravated pain and decreased range of movement. MRI scanning confirmed the recurrent tear and showed inflammatory changes and significant fluid pooling in the subdeltoid bursa area of all patients. The bursa effusion in one patient required draining by ultrasound-guided aspiration, but microbiology tests were negative for infection. Two patients underwent revision surgery to remove the implants and histological analysis of the debris demonstrated necrotic fibrinous material on a background of chronic inflammation [35]. A study using Zimmer patch in trapeziectomy also reported severe noninfectious inflammatory response shortly after surgery. Three implants retrieved during revision surgery revealed foreign body reaction in all samples. In this study the use of the Zimmer patch was also associated with poorer outcomes and its user was coupled with greater pain, lower grip strength and poorer function of the thumb [36]. Based on the above findings, the use of Zimmer patch is also not favored as it triggers an immune response that results in surgery failure.

TissueMend is manufactured by TEI Biosciences (Boston, MA, USA) and marketed by Stryker Orthopaedics (NJ, USA). It is a collagen base scaffold derived from fetal bovine dermis and produced using a series of procedures, which eliminates all cellular components, remodeling the fibers of the tissue. We were unable to find any publication in relation to the clinical outcome of TissueMend except a surgical technique paper recommending its use [37]. However, TissueMend has been reported to contain significantly higher genetic materials than Restore, GraftJacket and Cuff Patch [38], which raises the concern of possible implications in human applications.

CuffPatch scaffold is derived from porcine small intestine submucosa the same as Restore. CuffPatch collagen scaffold is reported to be 97% pure [39] and contains negligible amounts of DNA [38]. At the time of writing, neither clinical nor animal studies with regards to the efficacy of CuffPatch on promoting tendon repair could be found. However, animal study evaluating immune response of five commercial scaffolds revealed that it did elicit a significant cellular response from the host [40]. In addition, mechanical testing reported that the physical properties of CuffPatch is the weakest of the five commercial scaffolds tested [28].

OrthoADAPT (Pegasus Biologics, CA, USA) is a relatively new product approved by the FDA in late 2005 for marketing. It is also considered an acellular collagen scaffold derived from equine pericardium [41]. According to the degree of collagen cross-linking, OrthoADAPT was subdivided into three subtypes FX, PX and MX [41], which are intended for different applications in the reinforcement, repair and reconstruction of soft tissue in musculoskeletal procedures [41]. Mechanical testing demonstrated that OrthoADAPT is biomechanically equivalent to CuffPatch [41], which, as mentioned earlier, is the weakest amongst the five popular commercial scaffolds tested by Barber [28]. No animal

or clinical studies in relation to the efficacy of OrthoADAPT for tendon repair can be found. Only a technical paper mentioned the use of OrthoADAPT in transmetatarsal amputation [42].

BioBlanket (Kensley Nash Corp. PA, USA) is another newly approved scaffold for soft tissue reinforcement, including rotator cuff tear. It is a porous tissue matrix composed of a proprietary blend of fibrous and acid soluble collagens derived from bovine dermis. BioBlanket is thought to degrade slowly and is expected to last up to 1 year *in vivo*. In a sheep fascial defect model, the Restore was used as a control and was fully absorbed after 12 weeks, whereas the BioBlanket was still largely *in situ*. However, the same study also revealed that BioBlanket induced a greater inflammation response [43]. Whether the characteristic of slow degradation is beneficial to tendon healing still requires further studies under clinical application.

Shelhigh No-React Encuff Patch is a subcategory of Shelhigh No-React patch, which was previously used in abdominal surgery [44]. The brand name is better known for its artificial vascular valve products, which have been detoxified through a proprietary No-React process that makes the scaffold more resistant to adhesion degradation, dilation, infection and calcification [210]. Less favorable results related to the material have been reported in operations for congenital and emergency heart disease [45,46] and its efficacy on tendon injury has not yet been tested.

In summary, our review has identified and analyzed 18 clinical studies on four commercial biological scaffolds. Information regarding the study design, results and adverse events are summarized in TABLE 2. In total, 11 were supportive, six were against and two were neutral. Biological scaffolds largely designed for rotator cuff repair with 14 of the 18 studies were on rotator cuff. Restore is the most unpopular, with four out of six studies against its use on tendon repair due to high prevalence of postoperative noninfectious effusion caused by inflammatory response and foreign body rejection. On the other hand, GraftJacket appears to be the most efficient biological scaffold for tendon repair, with all efficacy studies supporting its use without incidence of major complications. Others scaffolds produced contradictory results, with information for and against their efficacy in tendon and ligament repair.

### Synthetic scaffolds

Synthetic scaffolds were popular in the 1980s and early 1990s. Materials such as polyester, polypropylene, polyarylamide, dacron, carbon, silicone and nylon fabric were fabricated into prostheses for tendon or ligament repair [47–50]. These synthetic ligaments and tendons have superior mechanical characteristics compared with biological scaffolds. However, their biocompatibility is very poor and caused numerous long-term complications, which attracted regulatory intervention at the end. Three commercial synthetic ligaments: the Gore-Tex Cruciate Ligament Prosthesis (WL Gore and Associates approved on 10 October 1986); the Stryker Dacrone Ligament Prosthesis (Meadox Medicals, Inc. approved on 30 December 1988) and the 3M Kennedy LADTM Ligament Augmentation Device (3M, USA approved on 7 May 1987) were initially cleared by the FDA for ACL reconstruction in

**Table 2. Clinical studies of commercial biologic scaffolds for tendon and ligament injury.**

Study type	Year	Tendon involved	Cases (n)	Follow-up (months)	Complications or procedure failure	Opinion	Ref.
<i>Restore™</i>							
Retrospective	2002	Rotator cuff	12	24	1 failed	Support	[10]
Retrospective	2004	Rotator cuff	11	6–10	10 failed	Against	[14]
Case report	2005	Rotator cuff	4	6	All 4 patients developed noninfectious effusion and failed	Against	[11]
Controlled trial	2006	Rotator cuff	30	14	9/15 scaffold group and 6/15 control group failed	Against	[13]
Technique note	2006	Rotator cuff	3	3–12	NA	NA	[111]
Controlled trial	2007	Rotator cuff	22	24	6/10 scaffold group and 7/12 control group failed	Against	[12]
<i>GraftJacket®</i>							
Case report	2004	Achilles	1	6	NA	Support	[21]
Technique note	2006	Rotator cuff	3	3–12	NA	NA	[111]
Retrospective	2007	Rotator cuff	16	26.8	3 failed	Support	[26]
Retrospective	2007	Achilles	9	20–30	No recurrent or complication	Support	[22]
Retrospective	2007	Rotator cuff	17	14	3 failed	Support	[25]
Retrospective	2007	Achilles	21	24 weeks	NA	Support	[23]
Retrospective	2008	Rotator cuff	16	26.8	3 failed	Support	[27]
Retrospective	2008	Achilles	11	20–30	No recurrent or complication	Support	[24]
<i>Zimmer® or Permacol™</i>							
Retrospective	2001	Trapeziometacarpal	16	NA	6 failed due to noninfectious effusion, foreign body rejection.	Against	[36]
Retrospective	2003	Rotator cuff	10	12	No recurrent and complication	Support	[34]
Case report	2007	Rotator cuff	4	3–6	Failed due to inflammatory response	Against	[35]
Retrospective	2008	Rotator cuff	10	3–5 years	2 failed, no complication	Support	[33]
<i>TissueMend®</i>							
Technical note	2006	Rotator cuff	NA	NA	NA	Support	[37]

NA: Not available.

the 1980s [218]. Although, these prostheses produce short-term satisfactory results, long-term studies have revealed that they caused many complications, such as implant degeneration, device failure, severe synovitis and inflammation response associated with foreign body reaction [51–56]. Subsequently, all three prostheses were retracted from market and a review of 117 cases of failed ACL reconstruction concluded that three factors contribute to the prosthesis failure: inadequate fiber abrasion resistance against osseous surfaces, flexural and rotational fatigue of the fibers, and loss of integrity of the textile structure due to unpredictable tissue infiltration during healing [57]. To date, the FDA still considers that all intra-articular prosthetic ligament devices pose significant risk to patients and places a strict requirement before conducting preclinical development [218]. Nevertheless, some synthetic scaffolds such as Gore-Tex, Lars, Leeds–Keio and Artelon were still frequently used in current medical practice. Their component and manufacture information are summarized in TABLE 1.

Gore-Tex materials are typically based on thermomechanically expanded polytetrafluoroethylene (PTFE) and other fluoropolymer products. Although it has been abandoned for ACL reconstruction due to severe complications [53,54,58], it is still widely used in all kinds of surgery ranging from plastic surgery [59] to general surgery [60], thoracic surgery [61], urological surgery [62–64], obstetric and gynecological surgery [65] and heart surgery [66]. The results were controversial; most of them were positive, although one reported a complication of carcinogenesis associated with long-term chronic inflammation response [63]. Nonetheless, satisfactory results have also been reported while using it for very large rotator cuff tear and patellar reconstruction. In a retrospective clinical study, 28 rotator cuff tear, size ranging from partial tear to more than 5 cm, were surgically repaired with Gore-Tex and followed for 72 months. Great improvement in pain relief, shoulder range of motion, muscle strength and Japan Orthopedic Associations scores were achieved at the final follow-up interview. However, three out of 28 cases have

been found to have recurrent tear between the rotator cuff and the scaffold, and revision surgeries were performed to close the gap [67]. In another study, Kollender *et al.* reported to use Gore-Tex strips for secondary patellar reconstruction of extensor mechanism after proximal tibia resection in seven patients. During a 2-year follow-up period, all patients had good-to-excellent functional outcomes without any incident of inflammatory response and infection [68].

Lars Ligament (Dijon, France) is a second-generation, nonabsorbable synthetic ligament device made of terephthalic polyethylene polyester fibers [69]. It has been approved by the health authorities of Canada, Europe and several other countries, but not the USA, for a range of applications including cruciate reconstruction, and Achilles tendon and acromioclavicular repairs. Promising results have been reported in several retrospective studies, which using Lars ligament for ACL reconstruction, patellar reconstruction and collateral ligament repair [69–73]. A prospective, randomized, controlled study on ACL reconstruction with a cohort of 53 (27 autograft, 26 Lars) reported that there were no differences regarding the failure rate (one in the Lars group), functional score and satisfaction rate between the autograft and Lars groups within the 24-month follow-up period [74]. Although minor complications such as knee stiffness have been reported in another study [72], severe complications such as synovitis, osteolysis and foreign body rejection, which were often seen in other synthetic scaffolds have not been found in Lars. Trieb *et al.* reported to find complete cellular and connective tissue ingrowth into a Lars prosthesis, which had been implanted 6 months earlier, thus concluded that Lars ligament causes minimum complications due to very high biocompatibility [75]. It appears that Lars ligament has excellent mechanical strength and biocompatibility to fulfill the requirements of long term implantation.

Leeds–Keio graft, also known as Poly-Tapes (Xiros plc, Neoligaments, Leeds, UK), has been a popular nonabsorbable synthetic prosthesis for tendon and ligament reconstruction since the 1980s. It is made of polyester (ethylene terephthalate) and was developed by the University of Leeds and the Keio University hence its name. Leeds–Keio was specifically designed for ACL reconstruction with stiffness of 200 N/mm that is similar to that of natural ACL [76]. Clinical results using Leeds–Keio ligament for ACL reconstruction were quite controversial, adverse events likes rerupture, tunnel enlargement, synovitis associated with polyester particles, greater pivot-shift and laxity were frequently reported in the 1990s [77–81] and early 2000 [82]. However, positive results have also been constantly published [83,84] and it seems that, along with the improvement of surgical technique, more favorable results have been achieved in the past 5 years [85–87]. Meanwhile, Leeds–Keio has also been used for other tendon repair such as rotator cuff tear [88], knee extensor mechanism reconstruction [89–93], Achilles tendon rupture [94], iliofemoral ligament repair [95], ankle lateral ligament repair [96]. All of these studies demonstrated favorable results and unanimously supported the use of Leeds–Keio for tendon and ligament reconstruction.

Artelon (Artimplant AB, Sweden) and Sportmesh (Biomet Sports Medicine, IN, USA) are made of biodegradable polyurethane urea polymer. It has been cleared by the CE and FDA for reinforcement of soft tissues, including rotator cuff, Achilles, patellar, biceps,

quadriceps. *In vitro* and *in vivo* animal studies conducted by the company suggested that Artelon fiber is slow degraded, biocompatible and capable of stimulating host cell ingrowth [97–99]. The only clinical study in relation to the efficacy of Artelon has been performed on trapeziometacarpal joint surgery. Ten patients had a spacer made from Artelon fiber inserted into their joint and another five patients (control group) were treated with standard arthroplasty. At 3 years after the surgery, no adverse events were observed and the median values for both key pinch and tripod pinch were better in Artelon spacer group than in the control group [100].

In summary, we have analyzed 29 clinical studies on synthetic scaffolds. Information regarding the study design, results and adverse events are summarized in TABLE 3. A total of 19 of them were supportive, seven of them were against and three were neutral. Synthetic scaffolds are largely designed for ACL reconstruction with 17 out of the 29 studies was on ACL. Lars ligament appears to be the most efficient synthetic scaffold for tendon repair with all efficacy studies supported its use. Leeds–Keio and Gore-Tex are well-established products with many studies examining their efficacy and producing mix results. Major complications reported in these studies included synovitis, osteolysis and foreign body rejection.

## Analyses

Scaffolds are manufactured to aid the restoration of normal function of an organ or tissue temporarily or permanently. There are several desirable characteristics:

- Adequate mechanical properties
- Ability to induce host tissue integration
- Appropriate biodegrading or absorbing rate, while being replaced by host tissue
- Biologically safe to the recipient
- Surgeon-friendly characteristic for easy fabrication into shape and size

## Mechanical requirement for commercial scaffolds

In tendon and ligament repair, mechanical properties of the scaffold need to be superior to host tissue, as early rehabilitation and physiotherapy are required to prevent joint stiffness after orthopedic surgery. The scaffold should be capable of shielding the native tissue from stress generated during functional excise until the regenerated tissue is strong enough to withstand the applied stresses along. However, mechanical properties of most scaffolds are dramatically lower than that of normal tendon and ligaments. Mechanical tests on human cadaver tendons and ligaments demonstrated that the ultimate strain of intact rotator cuff (supraspinatus) is  $1978 \pm 301$  N [101], ACL is  $1246 \pm 243$  N [102], patellar is  $3855 \pm 550$  N [102] and Achilles is  $5098 \pm 1199$  N (TABLE 4) [103]. Barber *et al.* demonstrated that the mean load to failure of GraftJacket (Extreme) is 229 N, Zimmer Patch is 128 N, TissueMend is 76 N, Restore is 38 N and CuffPatch is 32 N [28]. Synthetic scaffolds performed better, with Leeds–Keio ligament reaching  $780 \pm 200$  N [104] and Lars ligament reaching  $998 \pm 148$  N [105]. Although strength that

**Table 3. Clinical studies of commercial synthetic scaffolds for tendon and ligament injury.**

Study type	Year	Tendon involved	Cases (n)	Follow-up	Complication or procedure failure	Opinion	Ref.
<i>Gore-Tex</i>							
Retrospective	2000	ACL	123	5–11 years	26 rerupture, 50% loosen, 63% osteoarthritis	Against	[53]
Retrospective	2002	Rotator cuff	28	44 months	3 failed, no complication	Support	[67]
Retrospective	2004	Patellar tendon	7	24 months	None	Support	[68]
Retrospective	2005	ACL	17	13–15 years	15 patients had tibia bone tunnel widened	Against	[58]
Case report	2006	ACL	1	NA	Extensive periprosthetic osteolysis	Against	[54]
<i>LARS</i>							
Retrospective	2000	ACL	47	8–45 months	3 rerupture	Support	[73]
Prospective controlled	2002	ACL	27 Autograft 26 LARS	24 months	One revision in LARS group	Support	[74]
Retrospective	2004	ACL and LCL	21	27.4 months	NA	Neutral	[71]
Retrospective	2005	ACL	14	36 months	Stiffness in 5 patients	Support	[72]
Retrospective	2006	Knee extensor	22	44 months	Infection rate 18%	Support	[70]
Retrospective	2008	LCL	26	43 months	NA	NA	[69]
<i>Leeds-Keio</i>							
Retrospective	1991	ACL	20	2–4 years	Synovitis	Against	[81]
Retrospective	1992	ACL	25	5 years	NA	Support	[83]
Retrospective	1993	ACL	62	8–36	NA	Neutral	[79]
Retrospective	1995	ACL	24	2 years	3 rerupture	Against	[80]
Retrospective	1995	ACL	50	5–7 years	5 failures	Against	[78]
Retrospective	1999	ACL	82	40 days	NA	Support	[84]
Retrospective	2000	Ankle lateral Ligament	451 feet	5 years and 8 months	NA	Support	[96]
Retrospective	2000	Knee extensor	27 knee	5.9 years	NA	Support	[90]
Retrospective	2003	Knee extensor	12 knee	3 years	NA	Support	[89]
Case report	2003	Iliofemoral ligament	1	12 months	NA	Support	[95]
Retrospective	2004	ACL	18	13.3 years	28% rerupture 51% increase laxity	Against	[82]
Case report	2005	Medial patellofemoral ligament	2	6.1 & 8.5 years	NA	Support	[92]
Retrospective	2005	Knee extensor	15 knee	53 months	NA	Support	[93]
Case report	2005	Knee extensor	3 knee	12–48 months	NA	Support	[91]
Prospective, controlled	2006	Rotator Cuff	20 Leeds Keio 19 Autograft	2 years	NA	Support	[88]
Retrospective	2006	ACL	13	12 months	NA	Support	[87]
Retrospective	2006	ACL	30	24 months	Tunnel enlargement	Support	[86]
Retrospective	2007	ACL	50	10–20 years	6 rerupture	Support	[85]

ACL: Anterior cruciate ligament; LCL: Lateral collateral ligament; NA: Not available.

passes onto the tendon during daily activities may not necessarily reach the ultimate strain, it would be expected to be around 50%. Clearly the mechanical property of commercial scaffolds, especially biological ones needs to be greatly improved to meet the mechanical requirements.

#### **Degradation & tissue induction ability of commercial scaffolds**

It would be ideal for the scaffolds to induce tendon regeneration when undergoing degradation. In current literature, the degradation rate of different scaffolds varied dramatically. BioBlanket is reported to undergo slow degradation and is expected to last up to 1 year *in vivo*. Restore patch was completely degraded after 112 days implantation in mice while GraftJacket, CuffPatch and TissueMend were partially degraded, and Zimmer Patch was not degraded at all [40]. Synthetic scaffolds degrade much more slowly or not at all. A histological analysis of five knee joints after a minimum of 15 years following the ACL reconstruction with synthetic scaffold showed that the remain of scaffolds were clearly noted within the knee joint [56]. The tissue induction abilities of commercial scaffolds are not clearly defined as well. *In vivo* implantation experiments revealed that GraftJacket induced dense partially organized collagenous connective tissue formation; Restore device was completely replaced by mixture of organized muscle cells, collagenous connective tissue, and small islands of adipose connective tissue; Cuff Patch was replaced with little organization of new host connective tissue, TissueMend device induced adipose connective tissue accumulation; and Zimmer Patch was surrounded by a thin fibrous connective tissue capsule [40]. Induction ability of synthetic scaffolds is inferior to biological scaffolds. Guidoin *et al.* has examined 117 surgically failed ACL prostheses and found that healing inside the synthetic ACL was poorly organized, incomplete and unpredictable, as the extent of collagenous infiltration into the scaffold did not increase with the duration of implantation [57]. This may be due to the fact that synthetic scaffolds do not possess surface chemistry that is familiar to host tissue and therefore tissue ingrowth is suboptimal. Acidic by-products during synthetic scaffold degradation can alter the local environment and disrupt the proliferation of host tissue and cells also compromised the induction ability of synthetic scaffold. Biological scaffolds are generally

more capable of inducing host tissue ingrowth while undergoing degradation. However, the induction ability of biological scaffolds appears uncontrolled and nonspecific.

#### **Interaction between cell & scaffold surface**

Another key aspect of scaffold application is the interaction between scaffold surface and cells including promotion of cellular adhesion, proliferation and migration. At the beginning of cellular ingrowth, cells establish multiple attachment points through the interaction between transmembrane proteins and proteins at the scaffold surface. These attachment points are later strengthened by accumulating integrin receptors around each site and eventually form a focal adhesion that acts as a connection between the actin cytoskeleton of the cell and the surface. Only after the formation of focal adhesions and the spreading of cells on the surface, will the normal cell proliferation cycle and cell migration start [106]. Migration of cells is achieved by the detachment of focal adhesions at the trailing edge and the formation of new adhesions at the leading edge. Cells will generally move in the direction in which they can make the largest number of focal adhesions [107]. Porosity of scaffolds is also essential to cell attachment, proliferation and migration. It has been shown that pore sizes of 20  $\mu\text{m}$  are necessary for fibroblast in-growth, 20–125  $\mu\text{m}$  for skin regeneration and 200–300  $\mu\text{m}$  for fibrocartilaginous tissue in-growth [108]. The surface of biological scaffolds are mostly composed of natural type I collagen protein, which has a well-defined, inherent 3D structure. This unique topology creates a higher affinity to host cells and subsequently promotes cellular adhesion, proliferation, migration and tissue induction. By contrast, the surfaces of synthetic scaffold are composed of macromolecules form random coils and lack the well-defined structure that allows host cell to create a strong binding point and star growing. Although there are no studies directly comparing cellular behaviors on synthetic scaffold to biological ones, biological scaffolds would have more inherent advantages such as bioactive surface chemistry and favorable porosity for host cellular in-growth.

#### **Biocompatibility & adverse events**

Adverse events were frequently reported in the 47 clinical studies analyzed. Major concern about both biological and synthetic scaffolds is the biocompatibility and the inflammatory response

**Table 4. Mechanical property of commercial scaffolds and native tendon and ligament.**

Biological scaffolds	Mechanical strength (N)	Synthetic scaffolds	Mechanical strength (N)	Native tendon and ligament	Mechanical strength (N)
GraftJacket® (Extreme)	229 [28]	Lars ligament	998 ± 148 [105]	Rotator cuff (supraspinatus)	1978 ± 301 [101]
Zimmer Patch®	128 [28]	Leeds–Keio ligament	780 ± 200 [104]	Anterior cruciate ligament	1246 ± 243 [102]
TissueMend®	76 [28]			Patellar	3855 ± 550 [102]
Restore™	38 [28]			Achilles	5098 ± 1199 [103]
CuffPatch™	32 [28]				
OrthoADAPT™	27 [41]				

associate with foreign body rejection. A recent study examined the host response to five commercially biological devices showed acute and chronic host cellular response in all five scaffolds and multinuclear giant cells, associated with foreign body rejection were spotted in three of them [40]. Many long-term follow-up studies on synthetic scaffold have reported complications, such as infection, decreased stability, synovitis, osteolysis and osteoarthritis, which are direct or indirect results of inferior biocompatibility and host immune response [53,54,58,82,81]. Another concern is the risk of disease transmission associated with biological scaffolds. As all are manufactured from human or animal tissue, disease transmission to recipients is a theoretical concern, though no such case has been reported to date. Synthetic scaffold does not have such problem of disease transmission.

### **Advantages & disadvantages of biological & synthetic scaffolds**

Biological scaffolds are protein-based extracellular matrices that usually derived from human or animal connective tissues. Biological scaffolds have inherent advantage of bioactivities as they possess well-defined 3D surface proteins microstructure, which are familiar to the host cell. Its natural porosity provides much larger space for host cell attachment, proliferation, migration and assists gas and metabolite diffusion. All of these characteristics make biological scaffolds interact quickly with host tissue and induce new tissue formation faster. Although biological scaffolds are more bioactive, they also have several limitations:

- Low mechanical properties, which often results in failure of the surgery
- Nonspecific induction ability, which may impaired the quality of newly generated tissue
- Undefined degradation rate, which makes prediction of the repairing result much more difficult
- Variation in biocompatibility depending on the source of raw materials, which can cause inflammatory response and even implant rejection

Synthetic scaffolds are manufactured from chemical compounds, which permit better control over chemical and physical property leading to stronger in mechanical strength and consistency in quality. Such strong mechanical property is aimed to provide a permanent replacement of damage tissue such as ACL. However, as synthetic material can never be absorbed or integrate into host tissue, its biocompatibility is very poor. Results of poor biocompatibility include high incidences of postoperative infection, chronic immune response, which may result in aseptic effusion, aggravated pain and implant failure, ongoing osteolysis, which may destabilize the joint and fail the surgery, and potential toxic degradation byproducts, which may be the cause of synovitis and osteoarthritis.

### **Five-year view**

The regulatory agencies should pay more attention to the future development of commercial scaffolds. Under the current FDA 510k program, new commercial scaffolds do not have to provide

efficacy or adverse-event data to gain approval into the market. All that is required is for the manufacturer to produce evidence that the new material is substantially similar to a previously FDA-approved material. As a result of this fast-track program, many scaffolds were approved without any proper animal studies or evidence-based clinical trials. Consequently, complications were not revealed until late stages [13,14]. Tougher regulatory measurements should apply to ensure the safety and efficacy of these commercial scaffolds.

Most published studies are retrospective and case studies. Additional large and controlled research studies are needed to prove the efficacy and safety of these commercial scaffolds. Even in existing prospective control studies, selection criteria are often limited to gender, age and defect sizes. Other important factors like occupation, bodyweight and level of sporting demand should also been included when evaluating scaffold efficacy for musculoskeletal injury.

Current studies regarding tendon and ligament regeneration focus mainly on extracellular matrix reconstruction. Scaffolds are produced to mimic the tendon or ligament extracellular micro-environment to stimulate cell proliferation and tissue in-growth. The healing process at bone and tendon or ligament junction has been largely ignored. Tendon rupture, such as rotator cuff and Achilles tendon, often occur near the bone insertion region. The repair procedure often involves reconstruction of the junction and failure of surgery is frequently caused by osteolysis and scaffold pullout. All of the aforementioned suggests that the healing process of bone to tendon junction plays an important role in tendon and ligament regeneration. More study is needed to understand and promote the healing of bone tendon junction.

During manufacture of biological scaffolds, numerous chemical cross-linking agents, such as glutaraldehyde, polyepoxy compound, carbodiimide, genipin, isocyanate and proanthocyanidin were used to stabilize the collagen structure of the scaffold and thus maintain the mechanical properties. Zimmer, TissueMend, CuffPatch, Shelhigh, OrthADAPT and Bio-Blanket were cross-linked but not the Restore and Graftjacket. It appears that there is no obvious beneficial effect of chemical cross-linking scaffolds in relation to their clinical outcomes. Further study is warranted to prove the *in vivo* benefit of chemical cross-linking in biocompatibility and mechanical properties on the scaffolds.

Future technological development of new scaffolds should focus on improving the mechanical property and biological compatibility. One such advance is electrospinning technology. Electrospinning uses an electrical charge to draw very fine (typically on the micro- or nanoscale) fibers from a liquid [109]. It can easily produce nanostructured extracellular matrix scaffolds with controlled mechanical properties and architecture that structurally resembles the extracellular matrix of tissue, which provide a better environment for cell and tissue in-growth [109,110].

### **Expert commentary**

Many commercial scaffolds, both biological and synthetic ones, have been developed for tendon and ligament repair. Some of

them such as Graftjacket and Lars ligament, are very successful and well accepted by medical practitioners, but most of them have not been thoroughly tested. More prospective and controlled studies are needed to prove their superior efficacy over the traditional treatments. In future development, manufacturers should focus on improving the mechanical property and reducing the immunogenicity of the scaffolds.

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*The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.*

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#### Key issues

- The mechanical properties of commercial biological scaffolds are significantly lower than that of normal tendons and ligaments.
- Biological scaffolds are able to induce nonspecific tissue formation while undergoing degradation and their degradation rate needs to be better defined.
- Synthetic scaffolds have much stronger mechanical properties than biological ones; however, they induce very little host tissue in-growth and their biocompatibility remains very poor.
- Both biological and synthetic scaffolds can cause adverse events, such as noninfectious effusion and synovitis, which may result in the failure of surgery.
- Current literature ignores the fact that the bone to tendon junction plays an important role in the healing process; more study is needed to understand and promote the healing of bone-tendon junction.
- Most published clinical trials were retrospective, case reports. Additional large and controlled studies are needed to prove the efficacy and safety of these commercial scaffolds.
- Future development of novel scaffolds lies within the nanotechnology field.

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### Affiliations

- Jimin Chen, MB, MMS  
Centre for Orthopaedics Research, School of Surgery University of Western Australia, Room 2.33, 2nd Floor, M-Block, QEII Medical Centre, Nedlands, Perth, WA 6009, Australia
- Jiake Xu, MB, PhD  
Associate Professor, Centre for Orthopaedics Research, School of Surgery University of Western Australia, Room 2.33, 2nd Floor, M-Block, QEII Medical Centre, Nedlands, Perth, WA 6009, Australia
- Allan Wang, MBBS, PhD  
Associate Professor, Centre for Orthopaedics Research, School of Surgery University of Western Australia, Room 2.33, 2nd Floor, M-Block, QEII Medical Centre, Nedlands, Perth, WA 6009, Australia
- Minghao Zheng, MD, PhD, MRCPATH  
Professor, Centre for Orthopaedics Research, School of Surgery University of Western Australia, Room 2.33, 2nd Floor, M-Block, QEII Medical Centre, Nedlands, Perth, WA 6009, Australia  
Tel.: +61 893 463 213  
Fax: +61 893 463 210  
minghao.zheng@uwa.edu.au