Published Online January 4, 2010

Tendon augmentation grafts: a systematic review

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Introduction: Several biomaterials are available to bridge large tendon defects or reinforce tenuous tendon repairs.

Methods: We performed a comprehensive search of PubMed, Medline, Cochrane, CINAHL, and Embase databases using various combinations of the commercial names of each scaffold and the keywords 'tendon', 'rotator cuff', 'supraspinatus tendon', 'Achilles tendon', 'scaffold', 'biomaterials', 'extracellular matrix', 'substitute', and 'devices' over the years 1966–2009. All articles relevant to the subject were retrieved, and their bibliographies hand searched for further references in the context to biomaterials for tendon repair.

Results: Many biomaterials are available for tendon augmentation. Scanty evidence is available for the use of these scaffolds.

Discussion: The emerging field of tissue engineering holds the promise to use biomaterials for tendon augmentation. Preliminary studies support the idea that these biomaterials have the ability to provide an alternative for tendon augmentation. However, available data are lacking to allow definitive conclusion on the use of biomaterials for tendon augmentation. Additionally, the prevalence of postoperative complications encountered with their use varies within the different studies.

Conclusion: Rather than providing strong evidence for or against the use of these materials for tendon augmentation, this study instead generates potential areas for additional prospective investigation.

Accepted: December 1, 2009

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Keywords: tendon/scaffold/biomaterials/tissue engineering/extracellular matrix/sports

DOI:10.1093/bmb/ldp051

Introduction

Tendon disorders are frequent, and are responsible for much morbidity both in sport and the workplace.[1,2] Incomplete healing of tendon injuries can lead to marked dysfunction and disability, with compromised joint biomechanics and debilitating pain.[3,4] Clinical approaches to tendons rupture often involve surgical repair, which frequently implies working with degenerative, frayed tendon tissue, unable to sustain the rigors of normal activities, and may fail again.[5,6] Management of large tendon defects can present a dilemma to the orthopaedic surgeon. Tendon augmentation can provide a more effective management option producing a stronger construct.[6,7] Surgeons may tackle these injuries using autografts, allografts, xenografts and tendon prosthesis.[8] Allografts and xenografts have become increasingly popular for tendon and ligament repair to overcome the limited availability and donor site complication encountered with the use of autograft tissue.[9]

In the last few decades, biomaterials have become critical components in the development of effective new medical therapies for wound care.[8,10] Many new tissue engineered materials have been introduced: artificial polymers, biodegradable films and biomaterials derived from animals or human, using a combination of principles of engineering and biology.[8] As limitations of previous generations of biologically derived materials are overcome, many new and impressive applications for biomaterials are being examined.

Biological scaffolds are protein-based extracellular matrices that are usually derived from human or animal connective tissues.[9] Advantages of biological scaffolds are a well-defined 3D surface proteins microstructure (allowing host cell integration), and natural porosity (which provide much larger space for host cell attachment, proliferation, migration and assists gas and metabolite diffusion). These properties allow biological scaffolds to quickly interact with host tissue and induce new tissue formation faster than synthetic scaffolds. Limitations of biological scaffolds are low mechanical properties (often resulting in failure of surgery), non-specific induction ability, undefined degradation rate, variation in biocompatibility depending on the source of raw materials, which can cause inflammatory response and even implant rejection.[9]

On the other hand, synthetic scaffolds are manufactured from chemical compounds,[9] which permit better control of the chemical and physical properties leading to stronger mechanical strength and consistency in quality. However, biocompatibility of synthetic scaffolds is very poor, as they can never be absorbed or integrated into host tissue. High incidences of postoperative infection and chronic immune response have been reported with the use of such materials.[9]

Table 1 The most popular commercially available scaffolds.

Product	Company	Source	Cross-linking	Regulatory approval
Artelon® and Sportmesh™	Artimplant AB, Sweden and Biomet Sports Medicine (IN, USA)	Polyurethane urea polymer	Not applicable	Canada, Europe, FDA; Artimplant AB, Sweden
Bio-Blanket®	Kensey Nash Corporation (PA, USA)	Bovine dermis	Yes	FDA
CuffPatch®	Arthrotek (IN, USA)	Porcine SIS	Yes	FDA
Gore-Tex® patch WL	Gore and Associates, Flagstaff (AZ, USA)	ePTFE	Not applicable	FDA
GraftJacket®	Wright Medical (TN, USA)	Human cadaver dermis	No	FDA
'	Dijon (France)	Terephthalic polyethylene polyester	Not applicable	Canada, Europe
Leeds-Keio® or Poly-tape®	Xiros plc, Neoligaments (Leeds, UK); Yufu Itonaga Co., Ltd (Tokyo, Japan)	Polyester ethylene terephthalate	Not applicable	Canada, Europe, FDA
OrthADAPT®	Pegasus Biologic Inc. (CA, USA)	Equine pericardium	Yes	FDA
Permacol™	Zimmer (IN, USA)	Porcine dermis	Yes	FDA
Restore™	DePuy Orthopedics (IN, USA)	Porcine SIS	No	US FDA
Shelhigh No-React® Encuff Patch	Shelhigh Inc. (NJ, USA)	Bovine or porcine pericardium	Yes	FDA
TissueMend®	Stryker Orthopedics (NJ, USA)	Foetal bovine dermis	Yes	FDA

The most popular commercially available scaffolds are GraftJacket® (Wright Medical, Arlington, TN, USA), TissueMend® (Stryker Orthopedics, NJ, USA), Restore™ (DePuy Orthopedics, IN, USA), CuffPatch® (Arthrotek, Warsaw, IN, USA), Zimmer patch formerly known as Permacol™ (Zimmer, Warsaw, IN, USA), Shelhigh No-React® Encuff Patch (Shelhigh Inc., NJ, USA), OrthADAPT® (Pegasus Biologic Inc., Irvine, CA, USA), Gore-Tex® patch WL (Gore and Associates, Flagstaff, AZ, USA), Bio-Blanket® (Kensey Nash Corporation, PA, 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)[9] (Table 1). Porcine renal capsule matrix (RCM) has also been evaluated as a device to repair Achilles tendon injury, resulting equivalent to SIS and meriting further study in other tendon injury models.[11]

While the animal-derived products have been FDA 510(k)—approved for reinforcement of soft tissues, human-derived ECM grafts are classified as human tissue for transplantation under the Code of Federal Regulations (21 CFR, part 1270) and they do not require FDA approval for use.[8]

Rotator cuff and Achilles tendon injuries repair using these materials have been sparsely documented in the literature. The aim of this paper is to review the current state of knowledge in the field of biomaterials for augmentation of rotator cuff and Achilles tendon injuries.

Methods

Literature search and data extraction

We performed a comprehensive search of PubMed, Medline, Cochrane, CINAHL, and Embase databases using various combinations of the commercial names of each scaffold and the keywords 'tendon', 'rotator cuff', 'supraspinatus tendon', 'Achilles tendon', 'scaffold', 'biomaterials', 'extracellular matrix', 'substitute', and 'devices' over the years 1966–2009. All articles relevant to the subject were retrieved, and their bibliographies hand searched for further references in the context to biomaterials for tendon repair. Given the linguistic capabilities of the research team, we considered publications in English, Italian, French, Spanish and Portuguese. The search was limited to articles published in peer-reviewed journals. We excluded from our investigation case reports, literature reviews, and letter to editors. Article reporting on scaffolds for ligament repair were also excluded from the study.

Result

Commercially available biomaterials

Biological scaffolds

Biological scaffolds are obtained from mammalian (human, porcine, bovine and equine) tissues.[9] To remove any non-collagen components, thus minimizing the risk of host rejection while retaining its natural collagen structure and mechanical properties, small intestine submucosa (SIS), dermis and pericardium are processed through cascade steps, including general cleaning, removal of lipids or fat deposits, disruption of cellular and DNA materials, cross-linking and sterilization.[9]

The final scaffolds are composed mainly of naturally occurring collagen fibres, predominantly type I collagen, and several of them have a surface chemistry and native structure that is bioactive and promotes cellular proliferation and tissue ingrowth.[9]

Restore, GraftJacket, Zimmer, TissueMend, CuffPatch, Shelhigh No-React Encuff Patch, OrthADAPT and Bio-Blanket are considered biological scaffolds.[9]

Small intestinal submucosa xenografts

CuffPatch

CuffPatch (Organogenesis, Canton, MA, licensed to Arthrotek) is obtained from porcine SIS. It is composed of 97% collagen and 2% elastin. It has eight layers, it is acellular, and it is provided in a 6.5 by 9 cm sheet.[12] To ensure collagen content maturity, SIS is harvested from a closed herd in pigs weighing at least 205 kg.

The raw material is mechanically processed through a series of customized rollers and the inner and outer mucosal and muscular layers are removed to determine an uniform base product. The machined tissue is then cut and processed with a series of chemical cleansing solutions.

A non-detergent, non-enzymatic chemical cleaning protocol removes cells and cellular debris from SIS and protects the tissue architecture by controlling swelling of the collagen fibres.[13] Following lamination of the individual SIS layers, eight layers of the purified material are aligned along the long axis of the intestine and stacked on top of each other. The product is cross-linked with water-soluble carbodiimide. CuffPatch is nominally 0.6 mm thick, and although it is packaged hydrated, it should be rinsed before using.

Restore graft

The Restore graft (Depuy, Warsaw, IN) is a circular implant consisting of 10 not cross-linked layers of porcine SIS, 0.8–1 mm thick and with a 63 mm diameter. It is more than 90% collagen with approximately 5–10% lipids and a small amount of carbohydrate.[10,12] The layers are obtained from specific pathogen-free swine. The inner mucosa and muscular layers are manually removed. Individual SIS sheets are then cleansed and disinfected with peracetic acid and ethanol, and do not contain viable cells.

Ten individual layers are oriented at approximately 20° relative to each other and laminated together under a vacuum press to produce a 1 mm thick isotropic graft with sufficient strength and mechanical properties. Electron beam sterilization is performed after packaging.

Each lot is tested for bacterial endotoxins and mechanical strength. The implant is packaged dry and requires soaking for 5–10 min before use.

Dermal allograft

Graftjacket

Graftjacket (Wright Medical Technology, Inc.) is a commercially available acellular dermal matrix obtained from tissue bank human skin. It

is in compliance with the American Association of Tissue Banks guidelines for allograft material, and it is classified as human tissue for transplantation.

The skin is processed with a patented technique that removed epidermal and dermal cells, and the Graftjacket is then freeze dried to prevent the formation of ice crystals and to retain the native extracellular architecture and vascular channels.

Because it is rendered acellular during processing, it lacks many of the disadvantages typical of standard allograft tissue. The resulting patch is an acellular tissue composed of collagen types I, III, IV, VII, elastin, chondroitin sulfate, proteoglycans, and fibroblast growth factor. It has an intact basement membrane complex and preserved vascular channels to allow rapid infiltration of fibroblasts and vascular tissue, with minimal host inflammatory response.[10,14,15] It is recommended for tendon repairs, ligament augmentation, capsular reinforcement and periosteal covering.[10] It is commercially available in several forms. With an average thickness of 1.0 mm, it is available in 5 by 5 and 5 by 10 cm sheets. With an average thickness of 1.5 mm, it is available in 4 by 7 or 5 by 5 cm sizes. With an average thickness of 2.0 mm, it is available in a 4 by 7 mm size. It is packaged dry. Before use, the Graftjacket needs to be hydrated for at least 10–15 min.[10]

Allopatch

Allopatch HD is derived from human allograft skin processed using proprietary procedures developed by the Musculoskeletal Transplant Foundation. It is commercially available in several forms. With an average thickness of 0.8–1.7 mm, it is available in 5 by 5, 2 by 5 and 4 by 8 cm sheets. With an average of thickness $\geq$1.8 mm, it is available in 4 by 8 or 5 by 5 cm sizes. With an average thickness of 0.4–0.7 mm, it is available in a 2 by 5 cm size.

Dermal xenografts

The Zimmer Collagen Repair Patch

The Zimmer Collagen Repair Patch (Tissue Science Laboratories, Covington, GA, licensed to Zimmer) is a single layer porcine skin xenograft. It is an acellular cross-linked collagen sheet of cross-linked porcine dermis, 1.5 mm thick on average. After the initial mechanical processing to remove hair and epidermis, acetone is used to saponify the graft. Organic and enzymatic extractions are undertaken to remove fat, cellular material and soluble proteins. Hexamethylene diisocyanate cross-linking is then performed. The Zimmer Collagen Repair Patch may be stored at room temperature and is packaged hydrated.

Tissuemend

TissueMend (TEI Biosciences, Boston, MA, licensed to Stryker Howmedica Osteonics, Kalamazoo, MI, USA) is a single layer acellular, non-denatured collagen membrane derived from foetal bovine dermis, nominally 1 mm thick. The material is aseptically processed to remove cells, lipids and carbohydrates to reduce antigenicity and cleanse the tissue, and then sterilized in ethylene oxide. The product is 99% non-denatured foetal bovine collagen, which is not artificially cross-linked. It is available as a rectangular 5 by 6 cm implant and was tested in two thicknesses: 1.1 and 1.2 mm. It is lyophilized and packaged dry. The hydratation process requires less than 1 min.

Bioblanket

BioBlanket (Kensey Nash Corporation) Surgical Mesh is a porous tissue bovine dermal tissue matrix composed of a proprietary blend of fibrous and acid soluble collagens. It is lyophilized, crafted and cross-linked with proprietary processing methods to maintain mechanical and degradation profiles while the native tissue heals. Finally, the mesh is sterilized by irradiation. It has been FDA approved for the reinforcement and repair of a variety of soft tissues.

Pericardial xenograft

OrthoADAPT

OrthoADAPT (Pegasus Biologics) is an acellular biological scaffold derived from equine pericardium. It is cross-linked and sterilized with a proprietary process of biodegradable agents. It is not irradiated. It is approximately 90% type I collagen and 10% type II collagen. It is the thinnest graft available at 0.5 mm and is available as a 3 by 3 or 4 by 5 cm sheet or in strips that can be integrated into repairs.

Fascia lata

Allopatch

AlloPatch human fascia lata (Musculoskeletal Transplant Foundation) provides high peak load and tensile strength. A proprietary accellularization process leaves the human collagen matrix intact. Freeze dried and packaged flat, Allopatch rehydrates in minutes, and stores at room temperature.

Synthetic scaffolds

Synthetic scaffolds are made of polyester, polypropylene, polyarylamide, dacron, carbon, silicone and nylon.[9] They have superior mechanical characteristics compared with biological scaffolds, but very poor biocompatibility, and may cause several long-term complications.[9]

Shelhigh No-React® Encuff Patch

Shelhigh No-React® Encuff Patch (Shelhigh Inc.) is a subcategory of Shelhigh No-React Patch, which was previously used in abdominal surgery.[16] 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.[9]

Lars® ligament

The Lars® ligament (Dijon, France) is a second-generation, non-absorbable synthetic ligament device made of terephthalic polyethylene polyester fibres.[17] It has been approved by the health authorities of Canada, Europe and several other countries, but not the USA, for a range of applications.[9]

Leeds-Keio® or Poly-tape®

The Leeds-Keio® or Poly-Tape® (Xiros plc, Neoligaments, Leeds, UK; Yufu Itonaga Co., Ltd, Tokyo, Japan) is made of polyester (ethylene terephthalate) and was developed by the University of Leeds and the Keio University hence its name.[9] The Leeds-Keio was specifically designed for ACL reconstruction with stiffness of 200 N/mm, similar to that of natural ACL.[18]

Artelon® and Sportmesh™

The Artelon® and Sportmesh™ (Artimplant AB, Sweden and Biomet Sports Medicine) 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.[9] The device is supplied sterile in sheet form in double layer peelable packaging.

Gore-Tex® patch WL

The Gore-Tex® patch WL (Gore and Associates) is composed of the inert biomaterial expanded polytetrafluoroethylene (ePTFE). It features a microporous structure allowing for host-tissue incorporation.[19] It is elastic and resembles a dense sponge rubber.[20] The manufacturers have

reported an *in vitro* study on the strength of a 2 mm thick Gore-Tex soft tissue patch, as well as on that of Marlex Mesh, Prolene Mesh and Mersilene Mesh patches. The maximum force at rupture was 11.0, 4.1, 6.4 and 2.3 kg/cm, respectively.

Rotator cuff

Laboratory studies

Laboratory studies on biomaterials and rotator cuff are reported in Table 1.

Porcine SIS

Dejardin *et al.*[21] used porcine SIS in a canine infraspinatus injury model. Gross appearance, histological continuity and failure mode of the device evaluated at 3 and 6 months were similar to native tendon with a good integration between the new tendon and bone.

Zheng *et al.*[22] used Restore SIS in a rabbit supraspinatus injury model. Histologic evaluation at 8 weeks showed total replacement by collagen fibres in four of five samples, and no significant differences with the autologus implant, but the overall histology scores achieved by SIS implantation were still poorer than that of the autologous tendon implant.

Zalavras *et al.*[23] used an SIS device as an interpositional graft in a rat supraspinatus injury model. Histology and biomechanical testing at 6 and 16 weeks showed neovascularization and fibroblastic ingrowth in SIS-regenerated tendons, with an ultimate force to failure 78% of normal at 16 weeks. This was higher than in the defect group, which demonstrated an ultimate force to failure 34% of normal. The ultimate force to failure of the SIS-regenerated tendons approached that of the normal tendon at 16 weeks.

Schlegel *et al.*[24] used an SIS device to augment infraspinatus tendon repair in an ovine shoulder model. At 12 weeks, biomechanical testing and histology were performed. Histology addressed tissue healing at the bone–tendon interface. Although none of the patches were intact, the load-to-failure data did not indicate a significant difference between the augmented and non-augmented groups. However, the augmented group had significantly better stiffness than the non-augmented group. Histology showed that the infraspinatus tendon in all specimens inserted into the bone through a zone of fibrocartilage, although none of the patches were intact.

Perry *et al.*[25] used the Restore device in rat models of acute and chronic rotator cuff tear. Geometric measures and mechanical testing showed similar properties between the acute injury model and the injury repaired without SIS, while the chronic repair injury model

showed an increased modulus and a lower cross-sectional area of the healing tendon.

Chen *et al.*[26] used Restore and type I/III collagen bioscaffold as bioscaffold carriers for autologous tenocytes in a rabbit model of massive rotator cuff defect. At 8 weeks, the inflammatory reactions of both tenocyte-seeded bioscaffolds were dramatically less than with bioscaffold alone. In addition, bioscaffolds seeded with tenocytes produced a histological appearance similar to that of the positive control.

Graftjacket

Adams *et al.*[14] investigated the use of GraftJacket as an interpositional graft in a canine infraspinatus tendon injury model. Histologically, by 6 weeks cells infiltrated the control and experimental specimens. Biomechanically, by 12 weeks the strength of the experimental repair was equal to that of the control, but lower than that of the normal tendon. At 6 months, control and experimental specimens mimicked normal tendon structure grossly and histologically.

Fresh autograft fascia lata

Sano *et al.*[27] investigated the use of fresh autograft fascia lata as an interpositional graft in a rabbit supraspinatus injury model. At the fascia-bone junction, chondrocytes started to appear at 2 weeks after surgery, and increased rapidly thereafter in number and columnar organization. By 8 weeks, remodelling of direct insertion with fibrocartilage was almost complete, although a tidemark was not observed. The distribution of collagen types II and III showed a pattern similar to that of a normal supraspinatus tendon-bone insertion. The biomechanical properties were not reported.

Zimmer Collagen Patch

Nicholson *et al.*[28] evaluated Zimmer Collagen Repair (porcine dermal, PD) patch and Restore (SIS) patch in an *in vivo* sheep infraspinatus injury model. Bilateral infraspinatus tears were created and repaired in two groups of eight adult ewes. Each group (killed at 9 or 24 weeks) included 5 repaired with suture alone, 6 repaired and augmented with a (PD) patch, and 5 repaired and augmented with a SIS patch. At 9 weeks, the suture-only repair exhibited normal connective tissue formation. The PD patches were intact but were not fully integrated with surrounding tendon tissues at this time point. A large number of giant cells on the PD surface plus fibroblasts, macrophages and lymphocytes were seen. There was no connective tissue interdigitation at 9 weeks. The majority of SIS patches appeared to be completely resorbed. The area of the resorbed SIS patches was surrounded by primitive connective tissue containing macrophages, fibroblasts, woven bone and new

cartilage. At 24 weeks, failure loads were the same between groups, macrophages had disappeared from the PD groups, and integration of the PD patch into the surrounding tissue with vascular and fibroblastic invasion was seen.

Polycarbonate polyurethane

Cole *et al.*[29] investigated the biological response to a novel polycarbonate polyurethane patch used for tissue augmentation in a rat supraspinatus injury model. By 6 weeks, histology demonstrated no inflammatory reaction, and histomorphometry showed an average patch infiltration with connective tissue of 79.9%.

Polylactic acid

Koh *et al.*[30] augmented a sheep infraspinatus tendon repair with a polylactic acid scaffold. The augmented repair demonstrated a 25% greater strength than the non-augmented repair.

MacGillivray *et al.*[31] used polylactic acid patch to repair a goat infraspinatus defect model. There was no significant difference in load to failure between the shoulders repaired and augmented with polylactic acid patch and those repaired but not augmented. At 6 weeks, a cellular fibrous tissue occupied the patch, then maturing into a dense and homogeneous fibrous tissue with alignment of collagen between the scaffold bundles.

PLGA Nanofiber-based scaffold

Moffat *et al.*[32] designed a poly (lactide-co-glycolide) (PLGA) nanofiber-based scaffold for rotator cuff tendon tissue engineering. Rotator cuff fibroblasts cultured on the aligned scaffolds attached along the nanofiber long axis, while the cells on the unaligned scaffold were polygonal and randomly oriented. Quantitative analysis revealed that cell alignment, distribution, and matrix deposition conformed to nanofiber organization and that the observed differences were maintained over time. Mechanical properties of the aligned nanofibre scaffolds were significantly higher than those of the unaligned ones, and, although the scaffolds degraded *in vitro*, physiologically relevant mechanical properties were maintained, demonstrating the potential of the PLGA nanofibre-based scaffold system for functional rotator cuff repair. Moreover, nanofiber organization has a profound effect on cellular response and matrix properties, a critical parameter for scaffold design.

Comparison studies

Derwin *et al.*[15] compared the properties of GraftJacket TissueMend Restore and CuffPatch and their elastic moduli with that of normal

Table 2 Preclinical studies on rotator cuff.

Author	Product	Model	Tendon
Dejardin *et al.*[21]		Dog	Infraspinatus
Zheng *et al.*[22]	Restore	Rabbit	Supraspinatus
Zalavras *et al.*[23]		Rat	Supraspinatus
Schlegel *et al.*[24]		Sheep	Infraspinatus
Perry *et al.*[25]	Restore	Rat	Rotator cuff
Chen *et al.*[26]	Restore	Rabbit	Rotator cuff
Adams *et al.*[14]	GraftJacket	Dog	Infraspinatus
Sano *et al.*[27]		Rabbit	Supraspinatus
Nicholson *et al.*[28]	Zimmer Collagen Patch	Ewe	Infraspinatus
Cole *et al.*[29]	Polycarbonate polyuretane patch	Rat	Supraspinatus
Koh *et al.*[30]	PLA	Sheep	Infraspinatus
Mac Gillivray	PLA	Goat	Infraspinatus
Moffat *et al.*[32]	PLGA-nanofiber based scaffold	Laboratory study	Rotator cuff

infraspinatus canine tendon. Restore and CuffPatch had higher moduli than GraftJacket and TissueMend but that the elastic moduli of commercial extracellular matrices were one order of magnitude lower than that of canine infraspinatus tendons. The extracellular matrix moduli were one order of magnitude lower than the moduli (grip-to-grip strain) reported for different regions of the human infraspinatus tendon, suggesting that these extracellular matrices would likely carry only small loads.

Clinical studies

Clinical studies on biomaterials and rotator cuff are reported in Table 2.

Porcine SIS/restore

Iannotti *et al.*[33] tried to determine the effectiveness of porcine SIS to augment the repair of rotator cuff in humans. They randomized 30 shoulders with a chronic two-tendon rotator cuff tear (9 with a large tear and 21 with a massive tear of rotator cuff) that was completely repairable with open surgery to be managed with either augmentation with porcine SIS or no augmentation. The rotator cuff healed in 4 of the 15 shoulders in the augmentation group compared with 9 of the 15 in the control group ($P = 0.11$). The authors concluded that augmentation of the surgical repair of large and massive chronic rotator cuff tears with porcine SIS did not improve the rate of tendon-healing or the clinical outcome scores. On the basis of their investigation, they do not recommend using porcine SIS to augment repairs of massive chronic rotator cuff tears performed with the surgical and postoperative procedures described in this study.

Metcalf *et al.*[34] conducted a 2-year follow-up of 12 patients who underwent arthroscopic repair of massive chronic rotator cuff tears using Restore SIS as an augmentation device. Post-operative magnetic resonance imaging (MRI) scans showed significant thickening of the cuff tendon with the incorporation of the SIS graft in 11 patients. In 1 of 12 patients, clinical failure was observed within 12 weeks with complete resorption of the graft. There was no evidence of local or systemic rejection or infection in any patient. The mean post-operative University of California, Los Angeles (UCLA) score was 19.9 on a scale of 35, a significant improvement over the pre-operative score of 9.9 ($P < .01$), but the shoulder function remained far below normal in these patients. This study demonstrated improved post-operative outcomes for patients managed with Restore graft augmentation compared with their pre-operative condition. However, the lack of a control group makes it difficult to conclude that the functional improvements in the study were the result of SIS augmentation.

Sclamberg *et al.*[35] evaluated clinical and MRI at 6 months in 11 patients undergoing open repair of large or massive rotator cuff tears augmented with Restore. MRI showed a re-tear in 10 of 11 patients.

Zheng *et al.*[22] performed a study to evaluate the safety and efficacy of Restore™ SIS membrane. The Restore™ orthobiologic implant was examined by histology and the nested PCR technique using porcine immunoreceptor DAP12 gene to examine if SIS membrane contained porcine cells or DNA, respectively. The material was also implanted into mice and rabbits for the evaluation of biological reaction and inflammatory response. Restore™ SIS was found to contain multiple layers of porcine cells. Chloroacetate esterase staining showed that some of these cells were mast cells. Nested PCR of the DAP12 gene demonstrated that Restore™ SIS contained porcine DNA material. Subcutaneous implantation of Restore™ SIS membrane in mice, and in rabbits for rotator cuff tendon repair, showed that the membrane caused an inflammatory reaction characterized by massive lymphocyte infiltration. The authors concluded that Restore™ SIS is not an acellular collagenous matrix, and contains porcine DNA, contradicting the current view that Restore ™ SIS is a cell-free biomaterial, and that no inflammatory response is elicited by its implantation.

Walton *et al.*[36] compared a group of patients who had undergone rotator cuff repair with xenograft augmentation with a group repaired without augmentation. Four patients of the xenograft group showed a severe post-operative reaction requiring surgical treatment. Two years post-operatively, MRI documented retears in 6 of the 10 tendons repaired with a xenograft and in 7 of the 12 non-augmented tendons; the patients with a xenograft also had less strength than the controls and had more impingement in external rotation, a slower rate of

resolution of pain during activities, more difficulty with hand-behind-the-back activities, and a lower rate sports participation.

Zimmer Collagen Patch

Soler *et al.*[37] used Zimmer Collagen Patch as a bridging device to repair massive rotator cuff tears. After a good post-operative period, between 3 and 6 months the graft began to fail and the patients showed signs and symptoms of retear, with also signs of inflammation. MRI scans showed inflammatory changes, resorption of the graft, fluid pooling in the subdeltoid bursa and loss of continuity of the remaining graft material. Histology of the debris revealed necrotic fibrinous material on a background of chronic inflammation.

Badhe *et al.*[38] prospectively evaluated 10 patients with extensive rotator cuff tear treated with Zimmer Collagen Patch (Permacol). All patients experienced significant pain relief, and improvement in abduction power and range of motion. Ultrasound imaging at the final follow-up identified intact grafts in eight and disrupted grafts in two patients.

Graftjacket

Barber *et al.*[39] compared the failure mode of supraspinatus tendon repair with and without Graftjacket augmentation in a human cadaveric model. No significant displacement occurred during the cyclic phase, and no anchors failed. During the destructive testing phase, the mean load-to-failure strength of the control construct was 273 ± 116 N. The load-to-failure strength of the supraspinatus tendon augmented with GraftJacket was 325 ± 74 N. The constructs failed by two different mechanisms: tendon-suture interface failure (8/10 non-augmented repairs and 6/10 augmented repairs) and suture breakage (2/10 non-augmented repairs and 4/10 augmented repairs).

Bond *et al.*[40] treated 16 patients with massive rotator cuff tears with arthroscopic implantation of a GraftJacket allograft. At mean follow-up of 26.7 months, 15 of 16 patients were satisfied with the procedure. The mean UCLA score increased from 18.4 pre-operatively to 30.4 post-operatively. The mean pain score improved from 4.6 to 9.8 post-operatively. The mean constant score increased from 53.8 to 84.0. Statistically significant improvements were noted in pain, forward flexion and external rotation strength. MRI scans showed full incorporation of the graft into the native tissue in 13 patients.

Achilles tendon

Laboratory studies

Laboratory studies on biomaterials and Achilles tendon are reported in Table 3.

Table 3 Clinical studies on rotator cuff.

Author	Product	Tendon	Number of patients	Failure
Metcalf *et al.*[34]	Restore	Rotator cuff	24	1
Sclamberg *et al.*[35]	Restore	Rotator cuff	11	10
Zheng *et al.*[22]	Restore	Rotator cuff	4	4
Iannotti *et al.*[33]	Restore	Rotator cuff	30	6/15 control group and 9/15 scaffold group
Walton *et al.*[36]	Restore	Rotator cuff	24	7/12 control group and 6/10 scaffold group
Soler *et al.*[37]	Zimmer Collagen Patch	Rotator cuff	4	4
Badhe *et al.*[38]	Zimmer Collagen Patch	Rotator cuff	10	2
Barber *et al.*[39]	GraftJacket	Supraspinatus	17	3
Bond *et al.*[40]	GraftJacket	Rotator cuff	16	3

Polymer filamentous carbon composites

Foster *et al.*[41] used filamentous carbon fibre to replace the Achilles tendon in a rabbit model: carbon-induced 'neotendon' rapidly developed from young fibroblastic tissue outgrowths of the loose mesenchymal tissue of the perineurium and adventitia of the blood vessels in the adjacent neurovascular bundle.

Alexander *et al.*[42] used a composite material of filamentous carbon coated with an absorbable polymer, polylactic acid (PLA), as a tissue scaffold in rabbit Achilles tendons. The resumption of activity was possible with good histological and mechanical outcomes.

Isobutyl cyanoacrilate

Bonutti *et al.*[43] used isobutyl cyanoacrilate (ICA) in a rabbit Achilles tendon injury model: ICA alone exhibits reasonable strength *in vitro*. In combination with suture, ICA provides a stronger initial repair than either suture or adhesive alone.

SIS

Badylak *et al.*[44] used SIS in a dog model of Achilles tendon defect. By 12 weeks post-operatively SIS remodelled neotendons were stronger than the musculotendinous origin or the bony insertion ($>$1000 N), and showed organized collagen-rich connective tissue similar to the normal tendons. The dogs in which no SIS was implanted showed inferior strength. Immunohistochemical studies showed SIS degradation within the first 8 weeks, demonstrating that it behaves as a temporary scaffold for the organization of the connective tissue.

Zantop *et al.*[45] demonstrated that bone marrow-derived cells participate in the long-term remodelling of the Achilles tendon in a mouse model repaired with a SIS-ECM scaffold. The device recruited

a population of bone marrow-derived cells that participated in the long-term remodelling process.

Gilbert *et al.*[46] analysed the temporal degradation of the SIS device used for the repair of Achilles tendon in a dog model. There was a rapid degradation, with approximately 60% of the mass lost by 1 month after surgery, and complete resorption of the graft by 3 months. Histology at 3 months showed that the graft supported rapid cellular infiltration and host-tissue ingrowth, with a dense collagenous tissue with organization, cellularity, and vascularity similar to that of the normal tendon.

Porcine renal capsule

Suckow *et al.*[11] studied the utility of porcine RCM in comparison to SIS in a rat Achilles tenotomy repair model. Rats treated with RCM had slightly higher scores for degree of histologic change, suggesting a more rapid repair of the tenotomy site than in SIS treated. While remnants of SIS surrounded by macrophages and multi-nucleated giant cells were still present in some rats, remnants of RCM were not observed, suggesting more rapid incorporation of RCM.

Bone marrow stromal cell-seeded knitted PLGA fibre scaffold

Ouyang *et al.*[47] evaluated the effect of marrow-stromal cell (bMSC)-seeded knitted PLGA scaffold for Achilles tendon repair in two studies on rabbit models. In the first study, both the groups of tendons repaired with knitted PLGA graft (seeded with bMSC or not) showed good attachment of the scaffold to the proximal and distal ends of tendon 2 weeks post-operatively, but the volume of regenerated tissue was greater in the bMSC-seeded group. Immunoistochemistry showed that the cells were able to synthesize collagen. Histology showed more eosinphilic tissue formation inside and around the scaffold and more mature collagen fibres in bMSC/PLGA treated tendons than in the others. Perhaps PLGA scaffolds allowed cell infiltration, tissue formation, and were absorbed gradually after the formation of neotissue by the host. In the second study,[48] at 2 and 4 weeks the histology of the specimens bMSC/PLGA treated exhibited a higher rate of tissue formation and remodelling compared with specimens treated with PLGA alone, whereas at 8 and 12 weeks after the procedure. The histology of both groups was similar to that of the native tendon tissue. The wound sites of group bMSC/PLGA treated healed well, and showed no apparent lymphocyte infiltration. The tensile stiffness and modulus of group bMSC/PLGA treated were greater than those of the group treated with PLGA only.

Clinical studies

Clinical studies on biomaterials and Achilles tendon are reported in Tables 4 and 5.

Polymer filamentous carbon composites

Parsons *et al.*[49] used an implant composed of filamentous uniaxially aligned carbon fibres coated with an absorbable polymer in 48 patients with a rupture of Achilles tendon. This device acted as a scaffold for regrowth of collagenous tissue. The early strength of this repair was provided by the composite implant and by the rapid ingrowth and attachment of new tissue. All patients demonstrated continuous improvement during the first post-operative year, and a high level of function throughout the second year. Both repair of chronic and acute injury greatly improved.

Graftjacket

Lee[50] described the augmentation of chronic Achilles tendon rupture repair with GraftJacket, noting early return to activity and good plantarflexion strength.

Lee conducted two studies to evaluate Graftjacket as an augmentation device in Achilles tendon repair. In the first study,[51] nine patients with chronic Achilles tendon ruptures were followed up. There were no re-ruptures or recurrent pain at 20–30 months post-operatively, and the average return-to-activity time was 15.2 ± 1.7 weeks.

Table 4 Preclinical studies on Achilles tendon.

Author	Type	Model
Foster *et al.*[41]	Polymer filamentous carbon composites	Rabbit
Alexander *et al.*[42]	Polymer filamentous carbon composites	Rabbit
Bonutti *et al.*[43]	ICA	Rabbit
Badylak *et al.*[44]	SIS	Dog
Zantop *et al.*[45]	SIS	Mouse
Gilbert *et al.*[46]	SIS	Dog
Suckow *et al.*[11]	Renal capsule	Rat

Table 5 Clinical studies on Achilles tendon.

Author	Product	Number of patients	Failure
Parsons *et al.*[49]	Polymer filamentous carbon compsites	48	No increased morbidity with the use of the carbon implant
Lee *et al.*[50]	GraftJacket	1	None
Lee *et al.*[51]	GraftJacket	9	None
Lee *et al.*[52]	GraftJacket	11	None

In the second study,[52] 11 patients with acute tendon ruptures were followed up for 20 to 31 months. At 20 months, there were no re-ruptures or recurrent pain; the average return-to-activity time was 11.8 $\pm$ 0.75 weeks.

Barber *et al.*[53] demonstrated a significant increase in strength and stiffness of Achilles tendon repair augmented with GraftJacket in a human cadaver model (12.99 $\pm$ 5.34 N/mm versus 4.29 $\pm$ 0.83 N/mm of the control group).

Comparisons of different graft materials

Kummer *et al.*[20] examined four different graft materials (Gore-Tex Soft Tissue Patch, Graftjacket, bovine pericardium and an experimental graft material from Xylos Corporation) in chicken Achilles tendons. Compared with non-augmented suture, grafts increased suture fixation strength from 10 to 60% in shear and from 0 to 36% in pull-off with the bovine pericardium graft, providing significant improvement in both tests. In no cases (even unaugmented) did the suture pull directly through the tendon, but sliced along it, demonstrating that the interface between the suture and the tendon determines fixation strength. Grafts function by increasing the area, friction, and nature of this interface, not by acting as a barrier for suture pull-through.

Discussion

The emerging field of tissue engineering holds the promise to use materials in tendon injury repair, namely artificial polymers, biodegradable films and biomaterials derived from animals or human (ECM devices).[12] The most innovative strategy in tendon injury repair is the use of ECM matrices. In contrast to traditional polymeric and metallic orthopaedic devices, intended to restore mechanical function and remain unchanged for the life of the patient, ECMs are temporary scaffold aimed to enhance and accelerate the biology of tissue repair.[15] They undergo host cell infiltration and constructive tissue remodelling at variable rates.[54]

Potential advantages of the use of ECM grafts include the capability to decrease the *in vivo* mechanical forces on the tendon repair during post-operative healing, to prevent repair gap formation or failure, to allow host cell infiltration and ideally even enhance the biology healing, and to be replaced by organized host tissue over time. Additional research studies are required to verify these issues.

The ideal scaffold should induce host-tissue ingrowth and tendon regeneration during the process of degradation, which varies dramatically among the commercially available scaffolds.[55] The capability of inducing host-tissue ingrowth is superior when using biological scaffolds, even though this process appears uncontrolled and non-specific.[56]

The interaction between scaffold surface and host cells is a key aspect of the use of scaffolds for tendon reconstruction. In the first phase of cellular ingrowth, multiple attachment points are established by the cells through the interaction between transmembrane proteins and proteins at the scaffold surface,[9] later strengthened by accumulating integrin receptors, eventually forming a focal adhesion which acts as a connection between the actin cytoskeleton of the cell and the surface.[9] The cell proliferation cycle and cell migration start after the formation of focal adhesions and spreading of cells on the surface.[9] Cell attachment, proliferation and migration is facilitated by the porosity of scaffolds.[57]

The surface of biological scaffolds is mostly composed of natural type I collagen protein, which determines a higher affinity to host cells and therefore promotes cellular adhesion, proliferation, migration and tissue induction.[9] On the other hand, the surfaces of synthetic scaffold are composed of macromolecules lacking a well-defined structure that allows host cell to produce a strong binding point and start growing.[9]

Even though biological scaffolds are becoming more popular, clinical well-conducted human studies are lacking, and little data describing the complications or adverse events associated with the use of these products are available. ECMs fabricating in parallel with other materials may increase their mechanical properties, such as natural ECMs seeded with bone marrow stem cells or tenocytes.[47,48] However, clinical evidence in this field is scanty.

Major concern about both biological and synthetic scaffolds is the biocompatibility and the inflammatory response associated with foreign body rejection.[9] To decrease the bio-burden and the risk of inflammatory or foreign body reactions, all tissues, regardless of their origin, are extensively purified to remove proteins, cells and lipids. Some graft options have been artificially cross-linked to decrease antigenicity, by decreasing their sensitivity to collagenases. Although rare, aseptic, non-specific inflammatory reactions and foreign body-like reactions have been reported with certain xenografts.[10,12,22,58,59]

Aseptic reactions were reported in 16–22%[58] of implantations, always with negative aspirates and cultures, destroyed xenografts and histopathological evidence of inflamed granulation tissue with abundant neutrophils, but no foreign body reaction, as documented by the absence of organisms, crystals or giant cells.[10,58]

Valentin *et al.*[55] examined the host-tissue morphologic response to five commercially available extracellular matrix-derived biological scaffolds (GraftJacket, Restore, CuffPatch, TissueMend, Permacol) used for orthopaedic soft-tissue repair in a rodent model. Each device elicited a distinct morphologic response that differed with respect to cellularity, vascularity, the presence of multinucleated giant cells and organization of the remodelled tissue. More rapidly degraded devices such as Restore and autologous tissue showed the greatest amount of cellular infiltration, especially at the early time points. Devices that degraded slowly, such as CuffPatch, TissueMend and Permacol, were associated with the presence of foreign-body giant cells, chronic inflammation, and/or the accumulation of dense, poorly organized fibrous tissue.

Depending on the product, processing may involve acellularization treatment, chemical cross-linking, lamination of multiple layers or lyophilization.[8] These biomaterials have incomplete acellularization,[15,22] and the clinical implications are still not clear. Acellularization treatment aims to reduce antigenicity, by disrupting cells and removing water-soluble cellular proteins. Acellularization may also enhance host cell infiltration with phenotypically appropriate cells[60] and possibly prevent transmission of infectious genomic vectors.[61] Further biochemical and immunologic investigations are required to establish whether and how much acellularization treatment increases the safety and efficacy of these implants.

The use of biological scaffolds manufactured from human or animal tissue carries also the risk of disease transmission, which even though not reported to date, remain a theoretical concern. Obviously, there is no risk of disease transmission with the use of synthetic scaffolds.[9]

One of the advantages of biomaterials is that exogenous growth factors, gene therapy approaches or cell delivery can be used together with these biomaterials.

Several chemical cross-linking agents (i.e. glutaraldehyde, polyepoxy compound, carbodiimide, genipin, isocyanate and proanthocyanidin) have been used to stabilize the collagen structure of the scaffold, maintaining the mechanical properties. Clinical studies have not confirmed the expected beneficial effect of chemical cross-linking scaffolds. Further investigations are warranted to establish the *in vivo* benefit of chemical cross-linking in biocompatibility and mechanical properties on the scaffolds.[9]

As proposed by Chen *et al.*,[9] another reason of concern is that available scaffolds are produced to mimic the tendon or ligament extracellular microenvironment to stimulate cell proliferation and tissue ingrowth, largely ignoring the healing process at the enthesis. The repair procedure often involves reconstruction of the junction and failure of surgery is frequently caused by osteolysis and scaffold

pullout. Further investigations are required to better understand how to promote the healing of bone–tendon junction.

In conclusion, preliminary studies support the idea that these biomaterials can provide an alternative for tendon augmentation with an enormous therapeutic potential. However, available data are lacking to allow definitive conclusion on the use of biomaterials for tendon augmentation. Additionally, the prevalence of postoperative complications encountered with their use varies within the different studies. Rather than providing strong evidence for or against the use of these materials for tendon augmentation, this study instead generates potential areas for additional prospective investigation. Further investigations are required to evaluate the role of these materials in the clinical practice.

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