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Rotator Cuff Injuries: The Evolving Role of Tissue Engineering

P. S. Pastides[1] and W. Khan[1*]

[1]University College London Institute of Orthopaedics and Musculoskeletal Sciences, Royal National Orthopaedic Hospital, Stanmore, Middlesex, HA7 4LP, United Kingdom.

Review Article

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ABSTRACT

Aims: Rotator cuff injuries are a common injury associated with a combination of intrinsic and extrinsic causative factors. Although surgical reconstruction is a well established option, this is associated with variable re rupture rates. There is a growing body of interest in the potential tissue engineering in the management of rotator cuff injuries. This review aims to summarise the information in the literature on the evolving role of these techniques.
Study design: Review Article
Place and Duration of Study: University College London Institute of Orthopaedics and Musculoskeletal Sciences, Royal National Orthopaedic Hospital, Stanmore, Middlesex, HA7 4LP, United Kingdom.
Methodology: We reviewed the literature to identify studies on the use of tissue engineering therapy for the management of rotator cuff injuries
Results: There is an increasing body of evidence suggesting that stem cell techniques, augmented by the use of appropriate scaffolds and the influence of growth factors may promote healing in rotator cuff injuries.
Conclusion: Tissue engineering holds enormous promise to improve human health through prevention of disease and the restoration of healthy tissue functions. However to date, there is insufficient evidence to draw a solid conclusion. This field however presents a huge potential and warrants larger human studies to confirm any potential benefit.

Keywords: Rotator cuff; injury; scaffolds; growth factors; tissue engineering.

**Corresponding author: Email: wasimkhan@doctors.org.uk;*

1. INTRODUCTION

The shoulder joint is composed of three bones; the scapula, humerus and clavicle. The glenohumeral joint is the main joint of the shoulder. It is a shallow 'cup' that allows the head of the humerus a huge range of movement at the risk of joint dislocation. The extra stability of this joint arises due to the presence of the tendons and a group of muscles called the rotator cuff. The four muscles and associated tendons that contribute to shoulder movements and stability are the supraspinatus, infraspinatus, subscapularis and teres minor muscles. These muscles arise from the scapula and all insert onto the head of the humerus at the greater tuberosity except for subscapularis which insert into the lesser tuberosity. If one considers a further two muscles, the deltoid and teres major, then all six are named the scapulohumeral muscles.

As a result of the number of muscles and tendons, injuries around this region are common and constitute one of the musculoskeletal injuries (Shin, 2011).

The pathogenesis of rotator cuff tears is multifactorial. It is considered to be a combination of extrinsic impingement from structures surrounding the cuff and intrinsic degeneration from changes within the tendon itself (Meislin et al., 2005; Matthews et al., 2006). Extrinsic factors cause injury to the rotator cuff through the compression of the tendons by bony impingement or direct pressure from the surrounding soft tissue. In fact, it has been shown that in people involved in overhead sport or work, repeated extreme elevation in external rotation leads to contact between the insertion point of supraspinatus and the edge of the glenoid, thus initiating the cascade of primary and secondary events that end in rotator cuff tearing. Intrinsic factors Intrinsic arise due to direct injury to the rotator cuff by tensile overload, aging, or microvascular supply through traumatic, reactive, or degenerative insults to the rotator cuff (Walch and Boileau, 1992).

Most tears can be surgically repaired, the aim being to repair the anatomical structures in a tension free fashion (Nho et al., 2010). Outcomes are generally good, however re-rupture is well recognised. The factors associated with failure include patient age, smoking, tendon quality, size of defect and post operative rehabilitation (Lehman et al., 1995; Baumgarten et al., 2010). Re rupture rate varies with the literature and is estimated to be between 20% and 65% (Galatz et al., 2001; Gerber et al., 2000; Gulotta et al., 2011). In the case of failure, the success of revision surgery is low (Kowalsky and Keener, 2011).

A common reason of failure following repair is related to the sutures cutting through the tendons due to excessive tension at the repair. Although this can be improved by newer technologies and surgical techniques (Dunquin et al., 2011), there is still a high failure rate.

As a result there is growing area of interest in the use of tissue engineering to repair such defects. This may be synergistically used with scaffolds, growth factors, cell therapy and seeding.

2. MATERIALS AND METHODS

A thorough literature review was carried out to locate articles and studies describing tissue engineering techniques to aid in the treatment of rotator cuff injuries.

3. RESULTS AND DISCUSSION

3.1 Normal Tendons and Healing

Tendons are anatomic structures interposed between muscles and bones that transmit the force generated within muscle to bone, making joint movement possible (Ames et al., 2008). Tendons are constituted primarily of water, accounting for approximately 70% of their mass, whereas the dry mass of human tendons is approximately 30% (Sharma and Maffuli, 2005; Lewis, 2009). The basic elements of a tendon are collagen bundles, cells, and ground substance (or extracellular matrix). Collagen type I accounts for 65% to 80%, and elastin accounts for approximately 2% of the dry mass of the tendons (O'Brien, 1997). Tenocytes and tenoblasts lie between the collagen fibers along the long axis of the tendon. Collagen provides the tendon with tensile strength. It is arranged in hierarchical levels of increasing complexity, beginning with tropocollagen, a triple-helix polypeptide chain, which unites into fibrils, fibers (primary bundles), fascicles (secondary bundles), tertiary bundles, and the tendon itself. In a normal rotator cuff the most abundant collagen is type I. Type III collagen is weaker and it is only found in trace amounts (Maffuli and Longo, 2008; Longo et al., 2008). Based on their composition, tendons are hypocellular and avascular and hence have poor regenerative capabilities (Bray et al., 1996).

3.2 Tissue Engineering Strategies

3.2.1 Growth factors

The histologic lesion underlying overuse rotator cuff tendinopathy is a failed healing response, with haphazard proliferation of tenocytes, disruption of tendon cells and collagen fibers, and increased noncollagenous extracellular matrix. Recent attention has focused on the biological pathways by which tendons heal, leading to the identification of several growth factors (GFs) involved in this process (Olivia et al., 2011).

Platelet derived growth factor-BB (PDGF-BB), insulin-like growth factor-1 (IGF-1) and basic fibroblast growth factor (bFGF) have been used previously to promote tendon healing and tendon cell proliferation (Costa et al., 2006, Mishra and Pavelko, 2006). The use of growth factors to augment tendon repair in rotator cuff injuries and tendons in general is a fast evolving area.

Pauly et al. (2011) investigated the influence of growth factors bone morphogenetic protein (BMP)-2 and BMP-7 on tenocyte cell activity and matrix gene expression and production. Tenocyte-like cells were isolated from human rotator cuff tissue samples (supraspinatus and long head of biceps tendon) and incubated with BMP-2 (100-1000 ng/mL) and BMP-7 (100-2000 ng/mL), both alone and in combination. At days 0, 3, and 6, cell activity was assessed. They found that application of BMP-2 increased collagen type I production significantly but its expression only slightly. Cell activity was decreased in higher doses over time. For BMP-7, a significant increase in collagen type I production and expression, as well as increased cell activity, was observed. The addition of both factors resulted in decreased parameters when compared with BMP-7 alone. The expression of collagen types II and III, osteocalcin, and scleraxis was not significantly affected by application of BMPs

However some growth factors appear to have a negative effect on the healing of tendons. Kim et al. (2011) introduced isoforms of tissue growth factor (TGFβ) into transected

supraspinatus tendons in rats. They found that the TGF-β1 isoform delivered via an osmotic pump showed increased type III collagen production, indicative of a scar mediated response. In contrast to this, Kovasevic et al. (2011) found that the delivery of TGF-β(3) in an injectable calcium-phosphate matrix significantly improved strength of the repair at 4 weeks postoperatively and resulted in a more favorable collagen type 1 / collagen III ratio in rat models with supraspinatus detachments.

Seeherman et al. (2011) evaluated the ability of recombinant human bone morphogenetic protein-12 (rhBMP-12), administered in several carriers, to accelerate healing in a sheep model of rotator cuff repair. The maximum loads for the repairs treated with rhBMP-12 and a Type-I or Type-I/III collagen sponge were 2.1 times greater than those for the repairs treated with the Type-I/III collagen sponge alone. Changes in maximum stiffness followed a similar pattern. Histological evaluation demonstrated accelerated healing of the rhBMP-12-treated repairs compared with the untreated repairs.

Uggen et al. (2005) isolated cells from rat rotator cuff tendons and transduced the cells with the genes of either PDGF-ß or IGF-I by retroviral vectors. An *in vitro* model demonstrated an increase in collagen and DNA synthesis forming highly cellular tissue constructs by attaching to a polyglycolic acid scaffold. In addition when the cells were implanted into an experimental group of torn and then sutured rotator cuffs, this resulted in an almost complete repair.

Ide et al. (2009) investigated the effect of application of fibroblast growth factor (FGF)-2 on the tendon-to-bone remodeling of repaired supraspinatus tendon in rat madels subjected to bilateral detachment of the supraspinatus. FGF-2 (100 mg/kg) in a fibrin sealant or sealant alone was applied to the tendons. Histologically, at 2 weeks, FGF-treated specimens had significantly higher tendon-to-bone insertion maturing scores then untreated specimens ($P < .002$). At 4 and 6 weeks, the scores of FGF-treated and untreated specimens were similar ($P > .05$). Biomechanically, FGF-treated specimens were stronger at 2 weeks ($P = .001$); at 4 and 6 weeks, both specimens exhibited similar strength ($P > .05$).

In a sheep infraspinatus tear model, growth factors from bovine cortical bone extract (BMP-2 to BMP-7, TGF-ß1 to TGF-ß3, and fibroblast growth factor (FGF)) were implanted into healing rotator cuff with a type 1 collagen sponge (Rodeo et al., 2007). The augmented group showed increased bone and soft tissue volume and improved failure loads compared to the non-augmented group. They did note however that when the loads were normalised for tissue volume, there were no differences between the augmented and the control group. This may suggest that the growth factors may accelerate tendon healing but not actually the quality of tendon healing.

It is evident from the studies mentioned that several growth factors appear to have a advantageous role in rotator cuff healing. Therefore it is likely that growth factors may work synergistically to promote healing. Platelet rich plasma (PRP), includes many of the growth factors identified as essential for normal bone-to-tendon healing, such as TGF-β, bFGF, PDGF, IGF-1, vascular endothelial growth factor (VEGF), connective tissue growth factor and epidermal growth factor (Everts et al., 2006). It is may therefore act as a safe and potential augment in the healing process of tendons. (Maffulli et al., 2010)

Hee et al. (2011) investigated the role of platelet-derived growth factor-BB (PDGF-BB) in the healing process of tendons. An interpositional graft consisting of PDGF-BB and a type I collagen matrix was implanted in an ovine model of rotator cuff repair. A significant increase

in the ultimate load to failure was observed in repairs treated with 75 µg (1490.5 ± 224.5 N, P = .029) or 150 µg (1486.6 ± 229.0 N, P = .029) of PDGF-BB, relative to suture-only controls (910.4 ± 156.1 N) and the 500-µg rhPDGF-BB group (677.8 ± 105.9 N). The 75-µg and 150-µg PDGF-BB groups also exhibited increased tendon-to-bone interdigitation histologically.

Randelli et al. (2011) performed a double blinded randomised controlled trial and applied autologous PRP intraoperatively to arthroscopic rotator cuff repairs. At two year follow up they found that the treated group had less pain in the immediate post operative period. They also noted that the application of the PRP resulted in better healing of grade 1 and 2 tears.

Furthermore, some clinicians treat painful and inflamed rotator cuff tendons with local steroid injections which may further damage the tendons themselves (Bhatia et al., 2009). Baboldashti et al. (2011) looked at the use of platelet-rich plasma (PRP), a rich source of growth factors, as a healing agent to accelerate tendon repair. They exposed human tenocytes were exposed to different doses of dexamethasone with and without PRP. Dexamethasone reduced viable cell number without inducing overt cell death, but the number of senescent cells increased considerably. After co-treatment with 10% PRP, viable cell number increased significantly and the dexamethasone-induced senescence was markedly reduced. These findings suggest the potential for local administration of PRP to enhance tendon healing in patients undergoing glucocorticoid treatment.

3.2.2 Cell therapy

Advancements in the technical aspects of tendon repair have significantly improved the treatment of tendon injuries. Cell therapy may have the potential to improve clinical outcomes as well and attention has been directed towards the use of multipotential progenitor cells. Cells can be harvested, cultured and then promoted to differentiate into the desired cell type to aid tendon repair. Mesenchymal stem cells (MSCs) have potential applications in regenerative medicine and tissue engineering and may represent an attractive option for tendon repair and regeneration. They are autologous in nature and hence pose no immune risk to the host specimen upon implantation. They are relatively easy to harvest and are not associated with the ethical considerations attached to embryonic stem cells (Lui et al., 2011; Porada et al., 2011).

Gullota et al. (2010) experimented with 98 rats that underwent unilateral detachment and repair of the supraspinatus tendon. MSCs were harvested from 10 rats and the remaining animals received either MSCs in a fibrin carrier, the carrier alone, or nothing at the repair site. There were no differences in the amount of new cartilage formation or collagen fiber organization between groups at either time point. There were also no differences in the biomechanical strength of the repairs, the cross-sectional area, peak stress to failure, or stiffness.

Conversely, Pelinkovic et al. (2003) used genetically engineered highly purified muscle derived cells (MDCs), transfected with b-galactidose marker genes, and injected them into the tendinous part of surgically torn supraspinatus tendons in nude rats. From day seven the cell nuclei became spindle shaped, cells were integrated into the tendon collagen bundles, and the cells showed differentiation into vimentin-expressing fibroblastic cells. This may suggest that the rotator cuff tendon matrix and its original cellular components modulate the injected MDCs towards a fibroblastic phenotype. They conclude that the compatibility and ability of MDCs to differentiate into other cell lineages, such as fibroblasts, might therefore

have potential in tissue engineering applications, and in *ex-vivo* gene therapy for the treatment of rotator cuff lesions.

3.2.3 Scaffolds and augmentation grafts

Scaffolds and augmentation grafts are used to help off-load the repair in the immediate post operative period, and to improve the rate and quality of biological healing. The ideal scaffold should induce host-tissue in-growth and tendon regeneration during the process of degradation. In an analytical model for rotator cuff repairs, Aurora et al. (2010) found that approximately 70-80% of the load will be distributed to the repaired tendon, while the remaining 20-30% is distributed to the augmentation graft.

Combining stem cells with biomaterial scaffolds provides a promising strategy for engineering tissues and cellular delivery. These scaffolds are either biological or synthetic. Biological scaffolds are protein based extracellular matrices (ECMs) that are usually derived from human or animal connective tissue (Chen et al., 2009). The different components that make up the extracellular matrix provide a starting point for developing scaffolds based on natural biomaterials. These proteins and polysaccharides perform many roles *in vivo* and thus make such materials attractive for tissue engineering applications. Additionally, their natural origin often means that these materials contain sites for cellular adhesion and tend to be biocompatible. Synthetic scaffolds are manufactured from chemical compounds. Both have their advantages and disadvantages.

Biological scaffolds have the advantage of an established three-dimensional microstructure and natural porosity. It also interacts quickly with the host tissue. However, it may result in poor mechanical properties which may lead to surgical failure. It may also cause an inflammatory response and even rejection and is associated with a potential risk of disease transmission.

Synthetic scaffolds allow better control of the chemical and physical properties and thus may be stronger and more consistent in quality. However they display poor biocompatibility as they cannot be absorbed and may lead to chronic immune responses.

Using a rodent abdominal wall model, Valentin et al. (2006) compared several biological ECM scaffolds, methods of processing and methods of terminal sterilisation. One hundred twenty-six Sprague-Dawley rats were divided into six groups of twenty-one animals each. A defect was created in the musculotendinous tissue of the abdominal wall of each animal and then was repaired with one of five different scaffold materials (GraftJacket, Restore, CuffPatch, TissueMend, Permacol) or with the excised autologous tissue. Each device elicited a distinct morphologic response that differed with respect to cellularity ($p<0.001$), vascularity ($p<0.01$), the presence of multinucleated giant cells ($p<0.01$), and organization of the remodeled tissue ($p<0.01$) at or after the Day 7 time-point. 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. This finding was reinforced by Sandor et al. (2009) when comparing chemically cross-linked porcine dermis versus non-cross linked porcine small intestinal submucosa (SIS).

3.3 Animal Studies

The evidence surrounding the usefulness of stem cells in vivo is still being assembled. Some studies using animal models, have shown no benefit (Schlegel et al., 2006).

Other studies have showed more promising results. Porcine small intestinal submucosa (SIS) use to augment cuff repair has been the subject of a number of studies. Gumina et al. (2009) showed that a SIS regenerated 4mm supraspinatus tear in rats had a higher ultimate load to failure, toughness, stiffness, and yield strength than the defect group. Dejardin et al. (2006) similarly looked at an SIS scaffold in infraspinatus tears in dogs. At both 3 and 6 months, the SIS-regenerated tendons histologically mimicked normal tendon but were biomechanically weaker than normal tendons. Similar findindgs were noted by other authors as well (Zalavras et al., 2006; Perry et al. 2007).

Another biological adjunct to tendon repair that has been a subject of inestigation is chitosan. In an *in vitro* study Majima et al. (2005) used an alginate-based chitosan hybrid biomaterial to assess fibroblast adhesion of rabbit tendon fibroblast onto alginate polymer fibers versus the adhesion of the fibroblast onto alginate-based chitosan hybrid polymer fibers. Mechanically, the novel fiber has considerable tensile strength of more than 200 MPa and showed much improved adhesion capacity with fibroblast compared with alginate polymer fiber. Additionally, their morphologic studies revealed the dense fiber of the type I collagen produced by the fibroblast in the hybrid polymer fibres. Other authors also looked at using chitin fabric as a matrix for rotator cuff repair. Funakoshi et al. (2006) used chitin fabric as a matrix for rotator cuff regeneration. Chitin fabric was used to cover tears in infraspinatus tendons in a rabbit model. However, they found that the repaired tendon was mostly collagen type III and hence the biomechanical properties of the chitin scaffold were poor (Funakoshi et al., 2006).

One of the main findings that most authors using biological materials are the associated inflammatory response. On the other hand, synthetic materials would produce less reaction and thus result in a more biomechanically normal tendon repair. However 2 studies using polyglycolic acid (PGA) (Yokoya et al., 2008) sheets and polylactic patches (MacGillivray et al., 2006) in rabbits and goats respectively noted no significant improvements in the repaired rotator cuff acid sheet to augment rotator cuff repairs in white rabbits. Histologic improvement in tendon healing was demonstrated but this only correlated to a small improvement in tensile strength when compared to controls with another slowly absorbing synthetic material.

However, Santoni et al. (2010) used a polyurethane scaffold mesh in an attempt to confer greater biomechanical function relative to a nonaugmented repair after 12 weeks, in vivo, using a chronic ovine model of rotator cuff repair. Rotator cuff repair with the scaffold mesh in the chronic model resulted in a significant 74.2% increase in force at failure relative to the nonaugmented surgical control ($P = .021$). Apparent increases in stiffness (55.4%) and global displacement at failure (21.4%) in the mesh-augmented group relative to nonaugmented controls were not significant ($P = .126$ and $P = .123$, respectively). At the study endpoint, the augmented shoulders recovered 37.8% and 40.7% of the force at failure and stiffness, respectively, of intact, nonoperated controls.

This perceived benefit of using a synthetic scaffold was also shown using a woven poly-L-lactide device in a canine model (Derwin et al., 2009).

Nicholson et al. (2007) compared 2 types of allografts, cross-linked acellular porcine dermal (PD) patch and a porcine small intestine submucosa (SIS) patch, in ewes with bilateral infraspinatus tearss. At 3 weeks, sheep with suture repair and an SIS patch had significant elevation of plasma fibrinogen levels ($P < .05$) whereas sheep with suture repair and a PD patch elicited no elevation in plasma fibrinogen levels. At 9 weeks, the mean failure load was 201 +/- 60 lb for suture repairs, 182 +/- 63 lb for PD repairs, and 137 +/- 16 lb for SIS repairs. Within any individual sheep, the shoulder undergoing PD repair always had a higher failure load than the contralateral suture or shoulder undergoing SIS repair. At 9 weeks, macrophages were seen on all PD surfaces whereas most of the SIS materials were resorbed. At 24 weeks, failure loads were identical between groups but macrophages had disappeared from the PD groups, and integration of the PD patch into the surrounding tissue with vascular and fibroblastic invasion was seen. For the SIS group, diverse tissue types (including ectopic bone) were seen.

3.3.1 Scaffolds and cell or growth factor seeding

Attempts have been undertaken to combine techniques to aid rotator cuff repairs. The combination of fibroblast seeding, harvested from patella tendons, and a chitosan-based hyaluronan hybrid scaffold for rabbit infraspinatus tears resulted in improved tensile strength increased collagen type I production four weeks post-operatively compared to the non-cell seeded scaffold control group (Funakoshi et al. 2005).

Autologous cell infiltration into either biological or synthetic scaffolds was examined by Chen et al. (2007). Porcine small intestine submucosa (Restore) and type I/III collagen bioscaffold (ACI-Maix) were chosen as bioscaffold carriers for autologous tenocytes, which were then implanted as interposition grafts to reconstruct massive rotator cuff tendon defects in rabbits/ The tenocytes were harvested from patella ligaments. In situ reimplantation of the autologous rotator cuff tendon which was excised during the defect creation was used as a control. At 4 weeks, both tenocyte-seeded bioscaffolds displayed inflammatory reaction similar to bioscaffold-only cuff reconstruction, and the histological grading were inferior to control repair. However, at 8 weeks, inflammatory reaction of both tenocyte-seeded bioscaffolds were dramatically less than with bioscaffold alone. In addition, bioscaffolds seeded with tenocytes generated a histological appearance similar to that of the positive control.

In fact, autogenic cell constructs that have undergone gene therapy may have a more beneficial effect. Tenocytes transduced with PDGF-b or IGF-1 and seeded onto a PGA scaffold were used to augment the rotator cuff repair. The tendons transduced with PDGF-ß showed no improvement over controls augmented with PGA alone or simple repair. However, the fibroblastic cells transduced to express IGF-1 demonstrated an improvement in both strength and maximum load (Dines et al., 2007).

3.4 Clinical Studies

Only a limited number of studies in the literature currently describe human based clinical trials looking at the response of rotator cuff repair with biological augments.

Fourteen consecutive patients with complete rotator cuff tears (mean preoperative UCLA score of 12 ± 3.0) were fixed by transosseous stitches through mini-open incision, with subsequent injection of bone marrow derived mesenschymal cells (BMMSCs) into the tendon borders. These were harvested from the iliac crest just prior to surgery. Magnetic

resonance images (MRI) were acquired before and after surgery and evaluated by two musculoskeletal radiologists regarding new postoperative findings of patients treated with BMMSCs. After a minimum 12-month follow-up period, the UCLA score increased from 12 ± 3.0 to 31 ± 3.2. Clinical findings remained unaltered in the following year in all but one patient (13/14). MRI analysis after a 12-month follow-up period demonstrated tendon integrity in all cases (14/14), presence of low-signal intensity areas along the supraspinatus tendon and distal muscle belly in 8 cases (8/14), and high-intensity blooming small round artifact at the bursal and tendon topography in 11 cases (11/14). Six patients (6/14) showed formation of a high-signal intensity zone at the critical zone. Clinical findings remained unaltered in the following year in all but one patient. (Ellera Gomes et al. 2011).

In a randomised control trial, thirty shoulders with a chronic two-tendon rotator cuff tear were randomized to be treated with either augmentation with porcine small intestine mucosa (Restore) or no augmentation (Iannotti et al., 2006). Pre intervention magnetic resonance imaging showed that nine shoulders had a large tear and twenty-one had a massive tear. All patients underwent a magnetic resonance imaging scan with intra-articular gadolinium one year after the repair to assess the status of the rotator cuff. The rotator cuff healed in four of the fifteen shoulders in the augmentation group compared with nine of the fifteen in the control group ($p = 0.11$). Healing of the defects in both groups demonstrated a strong correlation with the patients' clinical scores undertaken pre and post intervention. The percentage change between the preoperative and postoperative patient satisfaction scores was 400% in the group with a healed repair, and 50% in the group with a failed repair ($p = 0.04$), leading the authors to recommend against this technique.

A further longitudinal study by Sclamberg et al. (2004), using Restore, found a rotator cuff re-rupture rate in 10/11 patients at 6 month follow up. They also noted no statistically significant difference in patient satisfaction scores and thus also do not recommend this treatment for rotator cuff repairs. Metcalf et al. (2002), also using Restore, came to the same recommendation. Conversely, Zheng et al. (2005) showed that Restore evoked an immune response causing significant inflammation and questioned its safety profile,

GraftJacket is a non-cross linked human dermis ECM that has been used in trials to treat rotator cuff injuries. Wong et al. (2010) treated 45 patients, suffering with massive rotator cuff tears, arthroscopically with GraftJacket al.lograft. Follow-up was a minimum of 2 years and analysis was performed using the 3 validated outcomes measurement scores (University of California (UCLA), Western Ontario Rotator Cuff (WORC), and American Shoulder and Elbow Surgeons (ASES) scores). The mean UCLA score increased from 18.4 preoperatively to 27.5 postoperatively ($P < .0001$). The average WORC score was 75.2, and the ASES score was 84.1 at the final follow-up. The authors concluded that the improved clinical outcomes warrant further evaluation. Dopirak et al. (2007) used the same graft in sixteen patients to span the tendon edge and bone defect being repaired. All patients had improved post-operative function. Radiographically three failures were demonstrated on MRI scans, two failed within the first three months and the third failed following a fall at four months. Two further studies using the same allograft found a similar re-rupture rate within the first year (Burkhead et al., 2007; Bond et al., 2008).

The same pattern and failure rates were reported by Badhe et al. (2008) using a Zimmer collagen repair, a cross linked porcine dermis ECM, but Soler et al. (2007) reported a total failure rate using the same graft in all patients they implanted it in.

In 2009, Rotini et al. (Rotini et al., 2009) initiated a prospective clinical study began where they implanted Acellular Human Dermal Matrix (AHDM) in 7 middle-aged patients affected with large rotator cuff lesions and tendon degeneration. After 1 year, of the 5 patients that were contactable, 3 patients had completely healed tears, 1 had a partial re-tear and 1 total recurrence with no adverse events noted.

It is clear that the results in the literature vary, however the number of high quality studies remains relatively small in number and size and so the perceive benefit may not yet be apparent.

4. CONCLUSION

The pathogenesis of rotator cuff injury is multifactorial. Degenerative changes, because of aging or overuse, in collaboration with other extrinsic factors contribute to the increase in frequency of this disorder. When conservative treatments have failed, surgical treatment may be offered. However failure post intervention is not uncommon. As a result, there is an increase in the potential added benefit of tissue engineering to augment rotator cuff healing.

Many growth factors and cellular processes are involved in normal tendon healing. It is probably not possible to clearly define the function of each in the complex inflammation and healing cascades. The addition of growth factors and/or reparative cells, either directly or via genetic engineering, has shown promising results for tendon regeneration in animal models.

Much research has been directed towards scaffold devices designed to augment and enhance tendon healing. Debate still surrounds the ideal scaffold, but Rotini et al. (2009) highlighted the essential criteria for the ideal scaffold: biological activity, biocompatible, reabsorbable, no risk of infectious disease transmission, mechanical strength, high suture retention quality, available in different sizes and thicknesses, easy handling in open and arthroscopic surgery, fit for augmentation and bridging and easy storage within the operating room. Furthermore, these devices may be improved with the use of genetic engineered or growth factors.

Tissue engineering holds enormous promise to improve human health through prevention of disease and the restoration of healthy tissue functions. However to date, there is insufficient evidence to draw a solid conclusion. This field however presents a huge potential and warrants larger human studies to confirm any potential benefit.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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