

Clinical and Biological Factors Affecting Rotator Cuff Repair: A Review Article

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Abstract

Rotator cuff tears are common and frequent source of shoulder pain and disability. Several intrinsic and extrinsic factors are identified to explain the etiopathogenesis of cuff tears and its healing potential. Cuff tear repair is successful, but a significant proportion of them fail to heal or re-rupture. Higher failure rate is seen in large tears, poor quality tendons with fatty infiltration and atrophy. Different repair, suture techniques and rehabilitation protocols have not shown any difference in clinical outcome when compared to each other. Recent literature has focused on rotator cuff repair with biological augmentation agents. Though the results are promising, further research is needed to identify effective biological augmentations that will enhance cuff healing and functional outcome after rotator cuff repair. Thus, this study reviewed the literature to describe the factors affecting cuff repair and emphasise on tissue regenerating techniques including growth factors, platelet rich plasma, stem cells and scaffolds.

Keywords: Rotator Cuff Tear; Rotator Cuff Repair; Rotator Cuff Healing; Shoulder Injury; Clinical Factors; Biological Factors

Abbreviations

RCT: Rotator Cuff Tear; BMP: Bone Morphogenic Proteins; PDGF: Platelet Derived Growth Factors; TGF- β : Transforming Growth Factor-Beta; bFGF: Basic Fibroblast Growth Factor; PRP: Platelet Rich Plasma; MSCs: Mesenchymal Stem Cells (MSCs); PTFE: Poly-Tetra-Fluoroethylene/Teflon

Introduction

Shoulder pain is the third most common musculoskeletal complaint [1]. Rotator cuff tears (RCTs) represent the vast majority of shoulder injuries in adult patients and are a common contributing factor to shoulder pain and occupational disability [2]. They were first reported by Smith JG in 1834 in the London Medical Gazette [3]. The incidence of the RCTs is also increasing with aging population. It is estimated that over 150,000 operations for RCTs repair are performed in the USA per year [4]. Despite this, the re-tear rate is up to 25% for small -to-medium tears and up to 90% for large tears [5]. The reported healing rate vary from 91% small tears to 6% for large/massive tears in some series [6].

The management of RCTs is complex, multifactorial and the best management option is still debated [7] as the pathogenesis of these tears is largely unknown [8]. Although improvements in instrumentation, suture anchor technology and repair techniques have evolved, a recent meta-analysis has shown that these are not related to improvement of clinical and anatomical results [9]. Due to the limited ability in healing, novel biomechanical strategies and biological augmentations (including growth factors, platelet rich plasma, gene therapy, tendon grafting, tissue engineering with mesenchymal and stem cells) have been proposed and are being investigated [2,8].

The purpose of this review is to outline the literature related to factors influencing healing after cuff tear repair (patient and surgeon related) and correspondingly summarise the approaches to improve tendon healing by applying tissue engineering.

Patient related factors

Intrinsic factors

Recent evidence suggests that most of the RCTs are caused by primary intrinsic degeneration [10]. Intrinsic factors affecting healing include quality of the tendon itself, age of the patient, micro-vascular blood supply, tendon overload, overuse or trauma [11].

Age

Oh, *et al.* [12] in a study of 117 patients and Cho, *et al.* [13] in 123 patients reported that increasing age (>65 years of age) was associated with poor outcome in both arthroscopic and mini-open cuff repairs. Chung, *et al.* [14] in a study of 108 patients found that age of the patient and fatty infiltration was associated with failure of cuff healing. According to Kumagai, *et al.* [15] as the human body ages, the properties of tendons are negatively impacted by process such as calcification, fibrovascular proliferation, degeneration, tensile loading and elasticity.

Vascularization

Codman described a hypo vascular zone at 10-15mm proximal to the insertion of supraspinatus tendon [16]. Goodmurphy, *et al.* [17] demonstrated that no significant difference in the microvasculature at the edge of the tear compared to the control specimens. They also concluded that the avascularity of the critical zone may be an artefact of techniques used during prior cadaveric studies. It remains unclear whether this hypo perfusion contributes to degeneration of the tendon. Hence literature is divided whether hypo-vascularity directly causes tendinopathy or not [11].

Tear size

Pre-operative cuff tear size is the main factor in determining long-term outcome of repair in relation to range of motion, strength and reoperation rate [11]. Large tears have lower healing rates after rotator cuff repair compared to small tears [18]. Significant improvement in functional outcome was reported in massive cuff repairs despite 40% failure rate [14]. Hence despite poor healing rates in large cuff tear repairs, satisfactory functional outcome has been reported in the literature.

Muscle-tendon gap

Tendon retraction or gap between cuff tendon edge and its insertion on greater tuberosity occurs due to muscle or tendon shortening [18]. Literature shows that the initial retraction in small tears is due to muscle shortening and in large/massive or chronic tears the tendon shortens. Meyer, *et al.* [19] reviewed 118 Shoulder MRIs and concluded that fatty infiltration correlates with increase in tear size, tendon shortening and muscle tendon gap. They also concluded that both preoperative muscle/tendon retraction and shortening negatively affect rotator cuff repair and functional outcome.

Fatty infiltration and cuff atrophy

Cuff healing and functional outcome are reported to be adversely affected by fatty infiltration and muscle atrophy [20]. Although fatty infiltration and muscle atrophy are both considered of same process, the outcome of cuff repair is independently predicted by them [21].

Goutallier, *et al.* [20] in a series of 220 shoulders, reported that recurrent tear rate was higher in patients with advanced fatty atrophy in the cuff muscles. Several studies have also reported that fatty infiltration and muscle atrophy are irreversible and lead to poor tendon healing and worse functional outcome even in the presence of successful repair [21,22]. However, Chung, *et al.* [14] reported 43% improvement in fatty atrophy after cuff repair in 191 patients. Liem, *et al.* [22] also concluded that there was no progress in atrophy or fatty infiltration in cases of intact cuff repairs whereas it progressed rapidly in re-tears and failed repairs.

According to Abtahi, *et al.* [18] fatty infiltration may stop after an intact cuff repair but will continue with re-tears. Muscle atrophy can potentially reverse in intact repair but will likely progress if the repair fails.

Patient factors

Patients who smoke are at greater risk of cuff disease and poor surgical outcome [23]. Nicotine not only causes vasoconstriction but also affects collagen concentration during the healing process. Mallon, *et al.* [24] concluded that pain relief, functional outcome after surgery are poor in smokers when compared to non-smokers in RCTs repair surgery.

Abtahi, *et al.* [18] reported that bone mineral density, vitamin D deficiency and hypercholesterolemia affect rotator cuff tendon healing after surgery. Beason, *et al.* [25] reported that diabetes has a detrimental effect on tendon healing in cuff tear models in rats.

Extrinsic factors

Shoulder impingement is one of the main extrinsic factor affecting rotator cuff healing. It is believed that acromial shape/angle and severity of rotator cuff tears are related [26]. According to Wang, *et al.* [27] the shape of acromion progress from flat to hooked as the age progresses. Coracoacromial ligament thickening and its changes occurring due to overuse activity also affect cuff tear and its healing [28].

Internal impingement, tight posterior capsule and aberrant scapular muscle activity including muscle deficits, abnormal posture directly affect shoulder kinematics, which could potentially affects the healing of the rotator cuff [11].

Surgical factors

Single vs double row repair

An ideal cuff repair construct would provide high initial fixation strength and minimize gap formation during healing [29]. Despite biomechanical studies showing increased load to failure and decreased gap formation in double -row repair as compared to single-row repair, clinical studies have failed to show any difference in functional outcome using either technique [18]. Some studies however have reported lower re-tear rates and improved functional outcome in patients with large to massive tears (> 3 cm) who underwent arthroscopic double-row repair [30].

Several studies have also compared knotted and knotless repair, different suture configurations and suture numbers on cuff healing and have reported no difference in functional outcome and repair integrity [31,32].

Overall double-row repair technique has improved healing rates, nevertheless functional outcome between double and single-row repairs are similar except for large/massive tears where double-row fixation may provide some functional advantage [18].

Post-operative protocol

Both basic science and clinical literature results are conflicting regarding which of the rehabilitation methods (delayed vs early) are better for satisfactory functional outcome. Anecdotally early aggressive rehabilitation is associated with higher re-tear rate. Contrary to this, Kim, *et al.* [33] found a lower re-tear rate in early aggressive rehabilitation group. Overall, early aggressive rehabilitation has shown better pain relief and range of motion in short term [18]. However, most studies show no difference at long term follow-up with regards to these functional outcome [34-36] except for slightly higher incidence of re-tear rate in early rehabilitation group especially in large/massive cuff tear repairs.

Biological factors

Tendon healing is a complex and orchestrated series of physiological events involving synthesis, migration and degradation of extracellular matrix components [10]. Tendon injuries normally heal through scar tissue formation, which can take up to 24 months to fully mature [37]. Another important controversy is the ability of the tendon to heal as the tendon tissue shows only a repair but no regeneration [38].

Given this limited ability for healing and high re-tear rate, novel biomechanical techniques and biological augmentations have been proposed to enhance rotator cuff tendon healing. Table 1 shows a summary of previous studies on biological factors and its outcomes.

Study	Human/Animal Study	Type of Study	Growth factor	Outcome measures assessed	Summary / Outcome
Gulotta, <i>et al.</i> 2011	Rats	Controlled lab study	BMP	Strength of repair	No benefit
Rodeo, <i>et al.</i> 2007	Sheep	Controlled lab study	Osteoinductive bone protein extract	Loads to failure	Greater failure loads. Poor quality scar tissue than true tissue regeneration
Uggen, <i>et al.</i> 2005	Rats	Controlled lab study	PDGF	Healing Load to failure	Near normal collagen alignment No difference
Kobayashi, <i>et al.</i> 2006	Rabbits	Controlled lab study	PDGF	Healing Load to failure	Highest concentration of PGDF in early repair phase No difference
Ide, <i>et al.</i> 2003	Rats	Controlled lab study	FGF-2	Healing	Accelerated remodelling
Manning, <i>et al.</i> 2011	Rats	Controlled lab study	TGF - β 3	Healing	Enhancement of local microenviroent. Accelerated healing process
Kovacevik, <i>et al.</i> 2011	Rats	Controlled lab study	TGF - β 3	Strength	Improved at 4 weeks stage
Weber, <i>et al.</i> 2013	Humans	Randomised Controlled Trial	PRP	Healing rates and outcome	No difference
Rodeo, <i>et al.</i> 2012	Humans	Randomised Controlled Trial	PRP	Healing rates and outcome	No difference
Barber, <i>et al.</i> 2011 Jo, <i>et al.</i> 2013	Humans	Case control Study	PRP	Healing and re-tear rates	Better healing (especially small tears) Lower re-tear rates
Hernigou, <i>et al.</i> 2014	Humans	Case control Study	MSC	Healing and re-tear rates	Better healing and lower re-tears (10 yrs f/u)
Barber, <i>et al.</i> 2012	Human cadavers	Cadaveric Study	GraftJacket	Functional outcome	Better ASES and Constant scores

Table 1: Summary of previous studies on biological factors and its outcomes.

Growth factors: PDGF: Platelet derived growth factor; BMP: Bone morphogenic proteins; bFGF: basic Fibroblast growth factor; TGF- β 3: Transforming growth factor-beta; Osteoinductive bone protein extract: BMP 2-7, TGF beta 1-3, FGF, PRP: Platelet Rich Plasma; MSC: Mesenchymal Stem Cells; GraftJacket - Collagen types I, II, IV, and VII, elastin, chondroitin sulfate, proteoglycans, and fibroblast growth factor.

Growth factors

Growth factors are signal molecules involved in the control of cell growth and differentiation and are active at different stages of inflammation. They are produced by inflammatory cells, platelets and fibroblasts [2]. Though RCTs healing occur through a process of inflammation, repair and remodelling, it results in reactive scar formation. Several growth factors released during the repair phase include bone morphogenic proteins (BMP) 12-14, platelet derived growth factors (PDGF), vascular endothelial growth factor, fibroblast growth factor, transforming growth factor-beta (TGF- β) and insulin like growth factor-1.

Rodeo, *et al.* [39] in their study on sheep model studied the effects of osteoinductive bone protein extract, which is constituted of bone morphogenic proteins 2 - 7, transforming growth factor -beta 1-3 and fibroblast growth factor. Though there was increased fibrovascular tissue in the bone tendon gap and subsequent greater failure loads, the scar tissue was composed of poor quality tissue than true tissue regeneration. In rats, BMP has shown no benefits with respect to the strength of repaired rotator cuff [40].

Several studies have studied the role of PDGF in tendon and ligament healing. Uggen, *et al.* [41] demonstrated near normal collagen alignment in rat rotator cuff repair model after PDGF delivery. Kobayashi, *et al.* [42] in their study on rabbits found that the highest concentration of PDGF occurs in first 2 weeks, which corresponds to the early repair phase. Though PDGF augmentation holds promise for augmenting tendon-to-bone healing [2] the precise role of PDGF dosing, timing and delivery methods remains unclear.

Basic fibroblast growth factor (bFGF) has been shown to have unique therapeutic potential in the early healing phase of human rotator cuff tendon tear during which there is still predominance of cell proliferation and lack of collagen synthesis [43]. In a study on rat rotator cuff tendon defects reconstructed with acellular dermal matrix, the local administration of FGF-2 showed accelerated remodelling [44].

TGF- β has also been identified as an important growth factor in bone-to-tendon healing. TGF- β is a family of cytokines that includes three isoforms. Of the three, TGF- β 3 holds promise to enhance the local microenvironment of rotator cuff repair [45]. Addition of TGF- β 3 to cuff repair has shown significant improvement in cuff strength at repair site at 4weeks after repair in a rat model [46]. Though these results promise the role of TGF- β 3 in improving tendon-bone-healing after repair, further studies are required to optimise the dosage particularly in human models.

Platelet rich plasma (PRP)

The use of PRP as a biological solution in cuff repair to improve healing has gained popularity over the last decade. PRP is a preparation of autologous plasma that contains a higher platelet concentration, allowing it to deliver a greater concentration of autologous growth factors, which may enhance cell proliferation of tenocytes and promote the synthesis of extracellular matrix [47]. There are several different forms of PRP depending upon their leucocyte concentration. The role of leucocytes in PRP is a controversial issue in the literature [2]. PRP can be applied either by direct injection or by application of PRP matrix scaffold on repaired tissues.

Randomized controlled trial by Rodeo, *et al.* [48] have shown no difference in healing rates and outcome with and without PRP in patients undergone cuff repair surgery. Weber, *et al.* [49] too in their RCT found no difference in the perioperative morbidity, clinical outcomes or structural integrity of cuff repairs. However, Barber, *et al.* [50] in a case control study and Jo, *et al.* [51] in their RCT have shown beneficial effect of PRP on cuff healing especially in smaller tears and reported statistically significant lower re-tear rates in PRP group when compared to the control group. Hence, there is currently no consensus on PRP application during rotator cuff repair and it is difficult to draw any definitive conclusions. Although PRP enables early healing for lateral epicondylitis, whether it enables early healing for rotator cuffs remains unknown [52].

Mesenchymal stem cells (MSCs)

Biologic augmentation of rotator cuff healing by the application of mesenchymal stem cells (MSCs) is being studied. Stem cells are defined as unspecialised cells with a self-renewal potential, which are able to differentiate into various adult cell types. Those, which can differentiate into various forms of mesenchymal tissue, are termed as mesenchymal stem cells [2].

The main source for the MSCs is bone marrow, which can be easily and safely harvested from proximal humerus or from synovial cells in the subacromial bursa during arthroscopic surgery and used in augmenting cuff repair [53]. The definitive role of MSCs in enhancing cuff tear healing process and strengthening the repair is debated in the literature due to conflicting results published. In rats, there was no improvement in the healing rotator cuff insertion site with the addition of MSCs, despite the evidence that MSCs were metabolically active [54]. However, Hernigou, *et al.* [55] in a study of forty-five patients reviewed the results of cuff repair with MSCs augmentation and compared with a control group, found statistically significant higher healing rate and lower re-tear rate in the MSCs group both at short term and at ten years follow-up.

Tendon augmentation graft/scaffolds

Graft augmentation provides stability for torn tendons and increases the rate of healing [52]. Several wide variety of products are available as biologic scaffolds from different companies in various forms. They can be divided into two broad categories: biologic (autografts, allografts, xenografts) or synthetic materials. The main principle is common among all these graft sources i.e. they consist of a protein based extracellular matrix and are composed primarily of type I collagen. Compared to tendon alone, augmentation grafts provide higher resistance to failure and minimise stress shielding [56]. Biomechanical and biological properties of these grafts vary depending on several factors like origin of the tissue, its preparation and augmentation techniques. Biologic scaffolds have the advantage of host cell integration, with a three dimensional protein microstructure and natural porosity. This allows a larger space for host cell attachment, proliferation and migration, and induces new tissue formation faster. However, the main disadvantages are its poor mechanical properties, unclear degradation rate, and variations in biocompatibility [57].

One of the widely used and studied biological scaffold is the GraftJacket (Wright Medical Technology, Inc, Memphis, TN). It is an allograft constructed from tissue bank human skin by removing the epidermal and dermal cells, and an acellular freeze-dried patch is made in different sizes/sheets with an average of 1.0 mm thickness. The main components of this GraftJacket include collagen types I, II, IV, and VII, elastin, chondroitin sulfate, proteoglycans, and fibroblast growth factor. The main advantage of this allograft is that of an intact basement membrane, and vascular channels, which aids in host incorporation [58].

In a randomised control trial by Barber, *et al.* [59] at a mean 2 year follow-up, patients with cuff repairs augmented by GraftJacket had significantly higher ASES and Constant scores with high percentages of patients in the augmentation group demonstrating intact cuff on MRI scans.

Several synthetic scaffolds include poly-tetra-fluoroethylene/Teflon (PTFE) felts, polyester grafts and Leed-keio grafts all of which mainly consists of polymer in different forms. The advantage of these are their strong mechanical properties, consistent quality, and no risk of disease transmission with use. However, main disadvantages are of biocompatibility leading to foreign body reactions, infection and decreased stability [58]. Though the results of these products are limited, there have been some positive results in animal studies and small clinical case series [60].

Conclusion

Multiple factors affect the rotator cuff repair healing process. Tendon healing after rotator cuff repair is a complex and highly regulated process. Higher failure rate are seen in large tears, poor quality tendons with fatty infiltration and atrophy. Different repair and regenerative techniques have been used to enhance and augment RCTs healing. Although double row technique of repair and delayed rehabilitation have shown slight advantage biomechanically, clinical outcomes are no different when compared to single row repair and early rehabilitation. Despite several biological factors responsible for cuff healing are studied, there is no definitive evidence in the literature supporting their regular use. Though stem cells therapy shows promising outcome in preclinical and clinical studies, further large randomised control trials and research on human tissue is required to establish its role in cuff tear healing.

Disclosure

According to our knowledge, there are no prior or duplicate publication of the same or very similar work. The manuscript has been read and approved by all the authors. Any potential conflicts of interest do not exist.

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