



## Review

# Current Perspectives on Rotator Cuff Disease

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**Abstract:** Rotator cuff (RC) disease, defined as any pathological state of the rotator cuff, is one of the most common shoulder conditions worldwide. It accounts for 70% of shoulder pain and dysfunction in adults and is the third most prevalent musculoskeletal disorder. Currently, the main issue with rotator cuff disease is that surgery represents the most common treatment performed. However, rotator cuff surgeries have a high failure rate positively correlated with the severity of the tear, and a high re-tear rate. This review will focus on the current research perspectives of rotator cuff repairs as well as new advances in the field. Current research is shifting its focus to target the healing and tendon repair process in an aim to decrease the failure rates. The bulk of research right now is within biologic methods based on growth factors, repair scaffolds, and stem cells that promote healing. Among this, researchers are continuously trying to improve surgical techniques. The complement of both methods should pave the way for much more effective, longer-lasting rotator cuff repairs.

**Keywords:** RC repair; biologics; arthroscopy



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## 1. Introduction

Rotator cuff (RC) disease, defined as any pathological state of the rotator cuff, is one of the most common shoulder conditions worldwide. RC disease accounts for 70% of shoulder pain and dysfunction in adults and is the third most prevalent musculoskeletal disorder [1–5]. The rotator cuff is comprised of four tendons—the supraspinatus, infraspinatus, subscapularis, and teres minor—that stabilize the glenohumeral joint [4–6]. Injury to any of these anatomical structures will be diagnosed as a rotator cuff injury. When dealing with rotator cuff injuries, two factors need to be considered in order to identify the proper course of treatment: the area affected (tendon vs. joint) and the etiology of the injury (lifestyle, age, intrinsic/extrinsic factors, muscle atrophy) [3,4].

RC tears are classified by depth and can be partial-thickness tears or full-thickness tears. In partial tears, the tear extends through part of the tendon but not through its entire thickness, that is, from the articular surface or from the bursal surface [3,4]. Contrary to this, a full-thickness tear extends throughout the entire thickness of the tendon, from the articular surface to the bursal surface [3,4]. A third type of tear is an intrasubstance/intratendinous tear in which the tear does not extend to the articular or the bursal surface [4]. Most of the time, these tears are treated through surgery, either open or arthroscopic surgery, which will be discussed in greater detail later.

Other rotator cuff conditions include tendonitis and impingement of the shoulder, the latter being the main cause of shoulder pain in adults [4,5,7]. These typically do not require surgical intervention. Shoulder impingement may occur through overuse of the shoulder or trauma through repetitive, overhead activities [4,7]. This may be by accident or depend on the person's lifestyle. Patients with occupations that require them to engage in consistent overhead movements are at a greater risk of having impingement, as are athletes. These conditions are usually treated with rest, physical therapy, cortisone injections, and/or anti-inflammatory medications [4,7]. At times, if the condition worsens and results in a tear, surgery may be required.

The etiology of rotator cuff injuries may be due to intrinsic factors, extrinsic factors, or a combination of both [3,4,8]. Intrinsic factors refer to the damage arising from the rotator cuff

itself. These tend to be degenerative in nature [3,8]. These include age-related degeneration, the presence of inflammation, oxidative stress, and dysmetabolism, among others [3,5,9–11]. The presence of micro tears throughout years of overusing the rotator cuff can eventually lead to full-thickness tears as well [3,8,9]. The forward flexion of the shoulder leads to inflammatory changes in the bursa, which contribute to the release of proinflammatory cytokine levels that further amplify the inflammatory response [10]. This leads to shoulder pain, especially at night, and shoulder dysfunction [2,10]. Gender disparities among rotator cuff tears are present. RC disease is more prevalent among women than men, and this could be due to a variety of hormonal and metabolic differences [12]. Hormones such as estrogen and thyroxin affect the tendon at a structural level, affecting both collagen and matrix metabolism. Thus, particularly in women, endocrine disorders such as diabetes mellitus, hypothyroidism, and hormone-related gynecologic disorders are associated with the development of RC disease [11,12]. Dysmetabolism and metabolic syndrome have over the last decade been found to play a role on the predisposition to RC tears. Thyroid disease and the presence of elevated lipid profiles, as is the case in metabolic syndrome, are associated with tendon ruptures. Thyroid disease and diabetes mellitus have been associated with a negatively altered tendon healing process leading to tears [11,12].

External factors include factors that originate outside of the joint area [3]. These can be anatomical, environmental, or due to an already-existing shoulder impingement [1]. This impingement may cause a change in the acromial shape of the individual, and this anatomical variation may make a patient more vulnerable to a rotator cuff tear [1,3,13]. The most common type of shoulder impingement, however, is subcoracoid. Subcoracoid impingement can later lead to subscapularis tears, a major anterior cuff tear [14,15]. Environmental and lifestyle factors also play a role, such as the frequency and intensity of activities involving overhead movements of the shoulder [7].

The problem with current treatments of RC tears is that the failure rate remains relatively high, and patients have a high possibility of a re-tear afterwards [2]. Due to this, current research is shifting its focus to target the healing and tendon repair process in an aim to decrease the failure rates. This, along with technical advances in surgery, holds the future of RC disease treatment. This review will focus on the current research perspectives of RC repairs as well as new advances in the field.

## 2. Current Treatments and Advances

Because RC disease is such a prevalent and bothersome condition that worsens with time, ensuring the appropriate treatments are given in a timely manner is imperative for the prognosis of the patient. There are several current treatments both surgical and non-surgical as well as many new treatment modalities. However, the main course of treatment remains surgical intervention. Current surgeries include subacromial decompression through acromioplasty or bursectomy, debridement of partial tears, or a RC repair [1,14,16]. These operations may be performed as open surgery, arthroscopic-assisted (mini-open) procedures, or arthroscopy-only procedures [1,15,17]. The most common of these is a rotator cuff repair through arthroscopy [1,14,16].

The treatment of RC tears has advanced throughout the years, particularly in the surgery realm. RC repair surgery went from an invasive to a minimally invasive option through the use of arthroscopic surgery. As mentioned, arthroscopic surgery is the main surgery technique used to repair the rotator cuff. It has many benefits, including being a minimally invasive procedure, short in duration, with a fast recovery rate for patients [14,15]. However, throughout the years, this procedure has been faced with some downfalls such as the increased possibility to re-tear, a high failure rate, and a reduced healing rate [2]. In fact, the incidence of re-tears after rotator cuff surgery are about 35% in small tears and up to 94% in larger tears, in which revision surgery would be needed [2,16]. Despite being an effective treatment, it continues to have a relatively high failure rate [2]. These are the main problems with rotator cuff repair today. Thus, advances in rotator cuff treatments are looking to improve the healing process and decrease the possibility

of a re-tear. The bulk of research right now is within biologic methods based on growth factors, repair scaffolds, and stem cells that promote healing. Among this, researchers are continuously trying to improve surgical techniques. The complement of both methods should pave the way for much more effective, longer-lasting RC repairs.

### 2.1. Patch Augmentations

One emerging technique that is currently being studied is the use of patch augmentation during RC repair. The aim of this is to amplify or “augment” the healing process. This technique uses a patch made of either synthetic or human-derived materials to provide structural support at the area of the repair [18,19]. By doing so, it should improve the fixing of the tendon to the bone and enhance tendon healing [18–21]. The goal behind rotator cuff repair is to attach the tendon to the bone and allow it to heal properly at its own pace. The reason why repairs usually fail is due to improper fixing of the tendon to the bone, causing the tendon to pull away from the bone leading to a re-tear [18–24]. The theory behind the use of patch augmentation is that by providing this support, the failure rate is expected to be reduced. The procedure consists of suturing the patch on top of the tendon-to-bone repair area [19]. This augmentation may be provided in two ways: on-lay, in which the patch is placed on top of a completed repair; or by bridging, in which it is used to fill a defect that the repair did not address [19–24]. This is a promising area in rotator cuff repair research, and in 2018 Cook et al. at the University of Oxford initiated a feasibility study for the use of these patches. Overall, the surgeons surveyed agreed that it was a rising procedure and admitted to having used a patch repair method in the past [18]. Over 20 patches have been approved for use both in the EU and in the US, and throughout this study, other centers were also testing the use of these patches on rotator cuff repairs [18]. A survey of surgeons from the British Elbow and Shoulder Society in the United Kingdom was conducted on the use of patch augmentations during rotator cuff repairs. Patch augmentation is increasingly being used by the National Health Service for RC repairs to reduce repair failures [25]. However, these patches were mostly used for large tears as opposed to minor or partial tears [25]. Current research indicates that patch augmentation is a rising technique for rotator cuff repairs. However, more research and clinical trials are needed to validate this. Nonetheless, it is an area of much interest right now with much data upcoming in the following years.

### 2.2. Biologics

The use of biologics to amplify the healing process is another highly active area in rotator cuff research. The biologic approach targets the microenvironment of the tear itself [26]. There are several current, emerging biological approaches to augment healing including the use of growth factors, platelet rich plasma, mesenchymal stem cells, and patches, which were previously mentioned [26].

The use of growth factors is being extensively studied. When a tear occurs, there is an upregulation of cytokines and growth factors present in the rotator cuff early in the healing process [26]. The aim is to amplify these signaling pathways and enhance the tendon healing process. There have been very little clinical studies conducted as this is a new field; however, animal models have shown that the delivery of these growth factors may improve the biology of tendon healing [26]. Several growth factors have been indicated to play a significant role in this process: vascular endothelial growth factor (VEGF), fibroblast growth factor-2 (FGF-2), platelet-derived growth factor (PDGF), and transforming growth factor-B (TGF-B).

VEGF is important in stimulating angiogenesis. It has not been directly studied in rotator cuff repairs; however, it has been studied in Achilles tendon repairs in rat models [16]. The studies indicated that the application of VEGF during the repair improved the tensile strength and enhanced healing [26]. Another study done in a rat model tested the addition of fibroblast growth factor-2. FGF-2 was applied to supraspinatus tears and was shown to accelerate and remodel the repair within the rotator cuff [26].

PDGF has been shown to be a critical growth factor in the healing process, with its concentration peaking 7–14 days post injury [26]. Although not extensively studied yet, this growth factor holds promise and much research is being invested into it as with TGF-B. TGF-B stimulates bone formation, which is expected to aid in the repair process as well [26]. There is enough preliminary data to suggest that further research on the use of growth factors for rotator cuff healing is necessary. However, there is much that remains to be studied. It is suspected that the ideal treatment would consist of a combination of growth factors, not just a single one used in isolation [26]. With that being said, researchers must investigate the efficacy of these treatments, but also what the ideal formulation and application process would be.

A widely used example of multiple growth factors being used at once is through the application of platelet-rich plasma (PRP). The use of PRP for rotator cuff healing is a rather recent endeavor. Through the use of PRP, a combination of growth factors is delivered to the repair area at once [26]. PRP releases many growth factors that contribute to the tissue repair process [26]. It has not yet met the expectations needed to become a widely used therapeutic for rotator cuff repair, but ongoing research aims to find the ideal formulation for PRP application in the rotator cuff setting [26].

Biologic scaffolds are currently gaining recognition as another possible therapeutic approach to aid in rotator cuff healing. Yiang Ma et al. are currently investigating the use of a biomimetic double-layer biofilm scaffold. This would be a biomimetic periosteum, which will combine growth factors and bioactive stem cells [27,28]. This scaffold would control the release of bone morphogenetic protein (BMP 2), VEGF, and PDGF to aid in the healing process [28]. This scaffold would be transplanted into the tendon–bone interface with the aim of promoting bone healing [28].

### 2.3. Stem Cells

A primary contributing factor of RC repair failure is prolonged tendon degeneration post repair [27]. Tissue engineering is a major field right now searching for ways to prevent these changes. Stem cell research in rotator cuff repairs is an emerging field with treatments arising from the use of mesenchymal stem cells.

Human mesenchymal stem cells (MSCs) can be engineered to differentiate into tendon tissue through the introduction of growth factors—TGF-B, BMP, and prostaglandins, among others [24]. These cells can be used alone or introduced to the repair site via scaffolds to induce tissue healing. Several published preclinical and clinical studies have already tried some of these methods and have provided promising results [24,28–30]. Bone marrow and fat are the most common sources of MSCs, and the subacromial bursa has been shown to be a viable source of mesenchymal stem cells for autologous rotator cuff repair [20,24]. In clinical studies this has been shown to be a safe method capable of enhancing rotator cuff regeneration [24]. A study conducted in 2019 by Cheng and Lui et al. tested a 3D-printed poly lactic-co-glycolic acid (PLGA) biocompatible scaffold with bone marrow-derived mesenchymal stem cells in the tendon-to-bone rotator cuff repair in a rabbit model. This study combined the use of a scaffold complemented with MSC to amplify the healing process, showing that the use of this technique in a rabbit model does in fact augment the healing process, making this a viable method for rotator cuff repair [31–33]. PLGA can be used to carry materials such as BMSCs, and they may upregulate osteogenic marker genes, further promoting the osteogenic differentiation of the BMSC [31–33].

There are limited studies and further questions to be answered, such as what the optimal time of delivery for these stem cells would be, the optimal number of cells to be injected, and if there are any potential off-target effects [24]. Thus, this is a highly active and promising area of research to aid in rotator cuff repair.

Preliminary studies have demonstrated that a type of MSC, adipose-derived stem cells (ASC), provide promising effects on cell proliferation, differentiation, and regeneration [27]. The first study to test the tenogenic differentiation capability of ASCs in an in vitro setting was done by Stanco et al. [31]. When culturing these cells and exposing

them to tenogenic induction they were able to upregulate tendon-related genes: scleraxis (SCX), COL1A1, COL3A1, collagen oligomeric matrix protein (COMP), and matrix metalloproteinase (MMP) [31].

It was found in rat models that ASC can prevent muscle degeneration and fatty infiltration and enhance rotator cuff healing through the activation of the AMPK signaling pathway [27]. The efficacy of ASC has been attributed to the ASC releasing vesicles called exosomes [27]. A study conducted by Zhang et al. studied this by testing the metabolic activity of adipose-derived stem cell exosomes on torn human rotator cuff tendons [27]. They found that the use of ASC proved to suppress the synthesis of catabolic cytokines, suppressed the synthesis of catabolic gene expression, and increased collagen type I/III gene expression [27]. All these mechanistic changes prevent the degenerative damage of the tendon and promote a healing environment. The significance of this study lies in the fact that it was the first study that looked at the effect of adipose-derived stem cells on torn human rotator cuff tendons, indicating their potential therapeutic use in the treatment of this condition [27].

Another stem cell population currently gaining recognition in the context of RC repair are fibro-adipogenic progenitor (FAP) cells [34]. These cells are resident progenitor cells within the muscles that can differentiate into adipocytes and fibroblasts [34]. Animal models have shown that these cells are present within the rotator cuff and their population expands after rotator cuff injury [34]. Thus, the repair process is dependent on the presence of these cells. In the case of patients with larger, full-thickness tears there is an increased concentration of FAP cells present [34]. These cells have not yet been studied in a human model, but it has been shown that the rotator cuff muscle has this endogenous stem cell source, which can be induced to differentiate into cells that may improve muscle function and quality after a rotator cuff repair [34,35].

#### *2.4. Muscle Advancement for Massive Rotator Cuff Tears*

The aforementioned treatment modalities are currently being examined primarily in the context of partial or minor tears. However, massive rotator cuff repairs require more advanced surgical procedures. Currently, repairs for these types of tears involve arthroscopic debridement, tendon transfer, partial repair, superior capsule reconstruction, and reverse shoulder arthroplasty [18]. Massive rotator cuff repairs face the problem of extremely high failure rates [36,37]. In order to address these issues more comprehensively, there have been advances not just through the use of biologics but in surgery techniques as well. Muscle advancement, in particular, has been used in maxillofacial surgery, oculoplastic surgery, and orthopedic surgery in transfer tendon insertion to improve elbow flexion [17,37–39]. Only recently it has been tested in the context of rotator cuff repair. The high amount of tension present post rotator cuff repair is associated with poorer clinical outcomes [36]. One possible way to relieve this tension is by manipulating the muscles through muscle elevation and advancement [33]. A clinical study conducted by Shin Yokoya et al. at the University of Hiroshima tested this methodology [36]. They completed arthroscopic rotator cuff repairs followed by supraspinatus and infraspinatus muscle advancement. The results were favorable, in that significant rotator cuff integrity was achieved up to two years post surgery, without any additional procedures [36]. Overall, this method reduced the failure rate and showed lower fatty degeneration [36]. One downfall was that there were few instances where the supraspinatus retracted medially. Nonetheless, this is indicative of a possible new approach that will aid in rotator cuff repairs in the future. This same group of researchers conducted a similar study a year later but this time combining muscle advancement with a biodegradable sheet. Patients underwent arthroscopic rotator cuff repair, followed by supraspinatus and infraspinatus muscle advancement and an addition of a polyglycolic acid (PGA) sheet [37]. The purpose of the PGA sheet is twofold: it provides structural support and a source of regeneration [37]. Using these reinforcing materials improves the healing capacity while at the same time reducing tension at the repair site [37]. The results showed that this method did reduce the failure rate and promoted a healing



environment [37]. The significance of this study lies in that this was the first study to test the combination of a surgical technique with a biologic, through arthroscopic rotator cuff repair, muscle advancement, and the use of a biodegradable. This exemplifies the future for rotator cuff disease interventions.

Advances in surgical techniques using modifications of pre-existing procedures in combination with newer techniques is another viable research area for rotator cuff repair. Morihara et al. performed this by using an arthroscopic-assisted Debeyre–Patte procedure [18]. The Debeyre–Patte procedure is a common muscle-advancement procedure used during rotator cuff repair that aims to alleviate the tension of the torn tendon to the greater tuberosities by dissecting the proximal origin of the rotator cuff muscles, followed by advancing the lateral stump and suturing it onto the greater tuberosity, and performing an osteotomy of the acromion [18]. This is a very invasive procedure with complications. Due to this, Morihara et al. proposed a modified Debeyre–Patte procedure in which the supraspinatus and infraspinatus were not detached, and their fascia connection to the rhomboids was maintained with no osteotomy of the acromion [18]. This procedure was conducted with assisted arthroscopy in order to minimize the large incision that would otherwise be needed [18]. This procedure demonstrated a significant improvement in the patient’s clinical outcomes [18].

### 3. Conclusions

Rotator cuff disease is a complex phenomenon, involving mechanistic changes at both the microscopic and macroscopic level, along with anatomical deviations that must be corrected through surgery. Currently, the main issue with rotator cuff disease is that the main form of treatment is surgery. However, these surgeries have a high failure rate positively correlated with the severity of the tear, and a high re-tear rate. Thus, current research aims to not only improve the efficacy of surgery techniques but also target the healing microenvironment and trying to promote regeneration at the repair site. Through the use of biologics, patch augmentations, and stem cells to complement the surgery, the aim is to improve the patient’s quality of life.

The reality is that treatment methodologies are not mutually exclusive. The future of rotator cuff repair lies in finding the optimal combinations of biologics and advanced surgery techniques to improve clinical outcomes, drastically decrease failure rates, and prevent re-tears.

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