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Review article

# The biology of rotator cuff healing

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ABSTRACT

Despite advances in surgical reconstruction of chronic rotator cuff (RC) tears leading to improved clinical outcomes, failure rates of 13–94% have been reported. Reasons for this rather high failure rate include compromised healing at the bone-tendon interface, as well as the musculo-tendinous changes that occur after RC tears, namely retraction and muscle atrophy, as well as fatty infiltration. Significant research efforts have focused on gaining a better understanding of these pathological changes in order to design effective therapeutic solutions. Biological augmentation, including the application of different growth factors, platelet concentrates, cells, scaffolds and various drugs, or a combination of the above have been studied. It is important to note that instead of a physiological enthesis, an abundance of scar tissue is formed. Even though cytokines have demonstrated the potential to improve rotator cuff healing in animal models, there is little information about the correct concentration and timing of the more than 1500 cytokines that interact during the healing process. There is only minimal evidence that platelet concentrates may lead to improvement in radiographic, but not clinical outcome. Using stem cells to biologically augment the reconstruction of the tears might have a great potential since these cells can differentiate into various cell types that are integral for healing. However, further studies are necessary to understand how to enhance the potential of these stem cells in a safe and efficient way. This article intends to give an overview of the biological augmentation options found in the literature.


## 1. Introduction

Pathologies of the rotator cuff (RC) are by far the most common cause of shoulder dysfunction and pain. In the presence of full thickness RC tears, RC reconstruction is a commonly performed surgical solution. Even though RC repair results in improved clinical outcome, several studies report failure of healing in up to 94% of patients [1].

The reason for these high failure rates may be due to intrinsic degenerative changes of the muscotendinous unit. Subsequent to a tear, the muscle retracts, but this muscular retraction is significantly less than the degree of tendon retraction that occurs at later stages [2,3] In the tendon, low cellularity, degenerative changes and poor blood supply of the enthesis are significant in the findings [4–8]. Whilst in the muscle, there is significant migration of inflammatory cells within the first few days of a tear and the muscle fibers undergo apoptosis [9,10]. In the ensuing weeks to months, this early response leads to muscular retraction, degeneration and atrophy. The progressive loss of muscle volume is due to a loss of sarcomeres in series that is associated with an increase in pennation angle, which causes an enlargement of the inter- and intramyofibrillar spaces [11,12]. If the muscle remains unloaded and retracted, the myogenic precursor cells may be reprogrammed into the adipogenic pathway, with mature adipocytes infiltrating the free inter- and intramyofibrillar spaces [13]. This phenomenon is termed fatty infiltration [9,14].

In the past two decades, orthopedic research has focused on biologically augmenting the RC reconstruction and therefore, improving healing at the tendon-bone interface as well as trying to stop muscular degeneration or even accomplish regeneration of the rotator cuff muscle. This biological augmentation has included applying different platelet concentrates containing growth factors, mesenchymal stem cells, scaffolds and a combination of the above. This review will provide an overview over the biological augmentation options based upon current evidence.

## 2. What is the healing response after rotator cuff tear?

The healing process is divided into three overlapping stages: inflammation (0–7 days), repair (5–25 days), and remodeling

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**Table 1**
Several factors that can be influenced by medication or change of lifestyle have been found. Recommendations for clinics are listed in this table.

| Factor | Evidence in literature | Recommendations |
|---|---|---|
| Age | Older age related with poor postoperative cuff integrity<br>However, age does not seem to be independent risk factor | |
| Smoking | Delay of tendon-bone healing in rat model<br>Inferior clinical outcome after repair in smokers | Discuss smoking cessation with patient preoperative<br>Goal: cessation or at least significant reduction of smoking |
| Diabetes mellitus | Animal model shows decreased biomechanical properties in diabetes mellitus rats<br>Patients with diabetes mellitus show higher postoperative complication rate, especially infections | Check blood glucose level preoperative<br>Goal: normal blood glucose levels pre- and postoperative |
| Use of NSAIDs | Basic research in rats suggests negative impact of NSAIDs on biomechanical and histological properties at early time-points | Reconsider common use of NSAIDs within the first 6 weeks postoperative. Some surgeons limit postoperative administration of NSAID to 3 days |
| Hypercholesterolemia | Cholesterol levels higher in patients with rotator cuff tear | Check blood cholesterol level preoperative |

(> 21 days) [15]. In the initial inflammatory phase, various cytokines released by the injured tissue attract inflammatory cells. These cells release other cytokines such as interleukin1-ß (IL1-ß) and tumor necrosis factor α (TNFα) that incite the inflammatory cascade [16]. These factors activate nuclear factor kappa B (NF-κB), which not only induces apoptosis in the musculotendinous unit but also causes muscle atrophy. Furthermore, NF-κB inhibits the regeneration pathway [10,17–19].

The unloaded musculotendinous unit post-tearing leads to the release and activation of pro-fibrotic factors from the surrounding extracellular matrix (ECM). These factors are members of the transforming growth factor beta (TGFβ) superfamily and are key regulators of gene expression in homeostasis. This early response to RC tear leads to apoptosis of tenocytes and degradation of muscle fibers. It allows cellular debris to be cleared and subsequent tissue regeneration to occur [20]. Vasoactive factors are released initiating angiogenesis and chemotactic factors are released stimulating cell proliferation [21]. Once the cellular debris have been evacuated, the monocytes get transformed to support new tissue formation [20]. In the muscle, these anti-inflammatory macrophages express myogenic regulatory factors (MRFs) [22], which in combination with other endocrine growth factors instigate the development mature myocytes from precursor cells [13,22]. In the tendon-bone interface, these anti-inflammatory macrophages seem to increase scar tissue formation rather than normal tendon tissue. This scar tissue initially consists of collagen type III. Subsequently, collagen type III is replaced by collagen type I, and therefore the collagen type I to III ratio increases[23]. The complex interplay of molecular and cellular mechanisms at the level of the enthesis, as well as in muscle, leads to further scar tissue formation at the enthesis and irreversible structural alterations in the RC. Research has therefore focused on altering this scar tissue response using different approaches.

## 3. Which biological factors may influence healing?

Several patients' specific factors have been shown to influence healing of the rotator cuff.

### 3.1. Age

The fact that increasing age may alter rotator cuff healing after rotator cuff repair has been reported by several authors [24–29]. Oh et al. [29] reported that age related with poor postoperative integrity in univariate analysis. Thus, multivariate regression showed that age was not an independent determinant for anatomical as well as functional outcome [29]. The only independent predictors found in this study were tear retraction and fatty infiltration. Even though increasing age has shown to negatively impact RC healing, several studies have reported good outcomes after RC repair in older patients [30,31]. Apart of age, several factors that can be influenced by medication or change of lifestyle have been found.

### 3.2. Smoking

Galatz et al. [32] demonstrated that nicotine impairs biomechanical as well as histological properties after rotator cuff tendon repair in a rat model. In a clinical study, a dose- and time-dependent relationship between smoking and the presence of rotator cuff tears was noted [33]. This data suggests that abstinence or at least a decrease in nicotine use might help to improve healing after rotator cuff repair.

### 3.3. Diabetes mellitus

Diabetes may have an impact on rotator cuff healing. Bedi et al. [34] reported that diabetes mellitus decreased biomechanical properties in a rat model. Chen et al. [35] reported a higher rate of postoperative complications, namely infections and to a lesser extent also failures.

### 3.4. Use of non-steroidal anti-inflammatory drugs (NSAID)

There is some basic research evidence that the application of NSAIDs postoperative may alter rotator cuff healing [36]. The common practice of administering NSAIDs should therefore be reconsidered during the first six postoperative weeks. After this period of time, NSAIDs do not seem to have an influence on healing and there is evidence that they positively influence the remodeling of collagen matrix during that time [37].

### 3.5. Hypercholesterolemia

There seems to be a relationship between an individuals' lipid levels and tendon pathologies [38]. Therefore the question rises, if high serum cholesterol levels should be treated before rotator cuff surgery.

### 3.6. Vitamin D deficiency

Even though animal studies suggest that low levels of vitamin D may negatively influence early healing at the rotator cuff repair site [39], in a clinical setting, no correlation was found with the severity of rotator cuff tear or the retear rate [40]. Recommendations for clinics are depicted in Table 1 concerning these risk factors.

## 4. It is possible to augment the rotator cuff enthesis?

RCT occur predominantly in the enthesis, the transition zone between the tendon and the bone. The tendon-bone junction is

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