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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 However, age does not seem to be independent risk factor	
Smoking	Delay of tendon-bone healing in rat model Inferior clinical outcome after repair in smokers	Discuss smoking cessation with patient preoperative Goal: cessation or at least significant reduction of smoking
Diabetes mellitus	Animal model shows decreased biomechanical properties in diabetes mellitus rats Patients with diabetes mellitus show higher postoperative complication rate, especially infections	Check blood glucose level preoperative 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

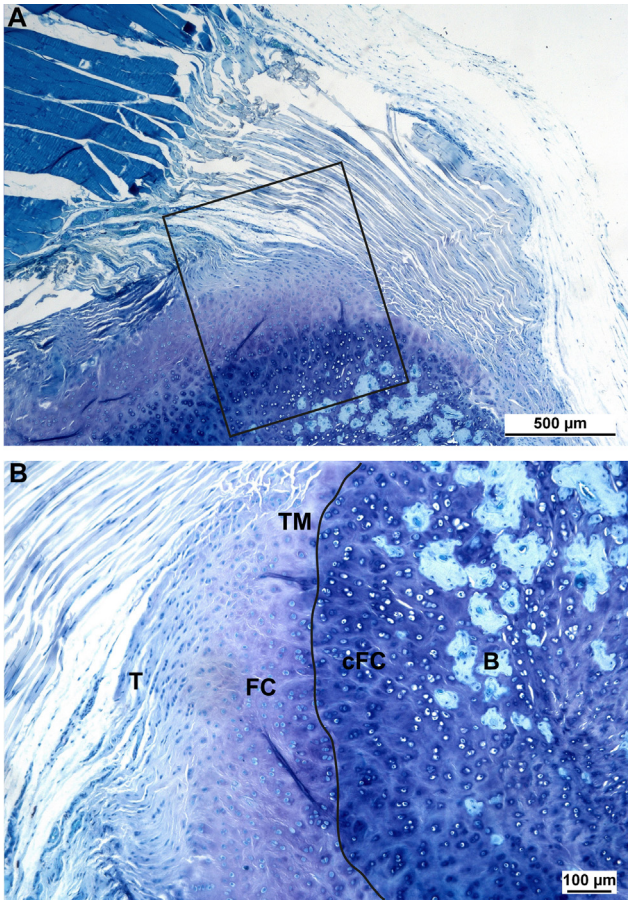

Fig. 1. A and B. A physiologic structure of an enthesis consists of 4 zones which are visible in the left picture (A, 500 µm). Details of the enthesis (B, 100 µm) with the tendon (T), the unmineralized fibrocartilage (FC) the mineralized fibrocartilage (cFC) and the bone (B). The tidemark (TM) as the transition from cartilaginous to calcified fibrocartilage is marked with a black line.

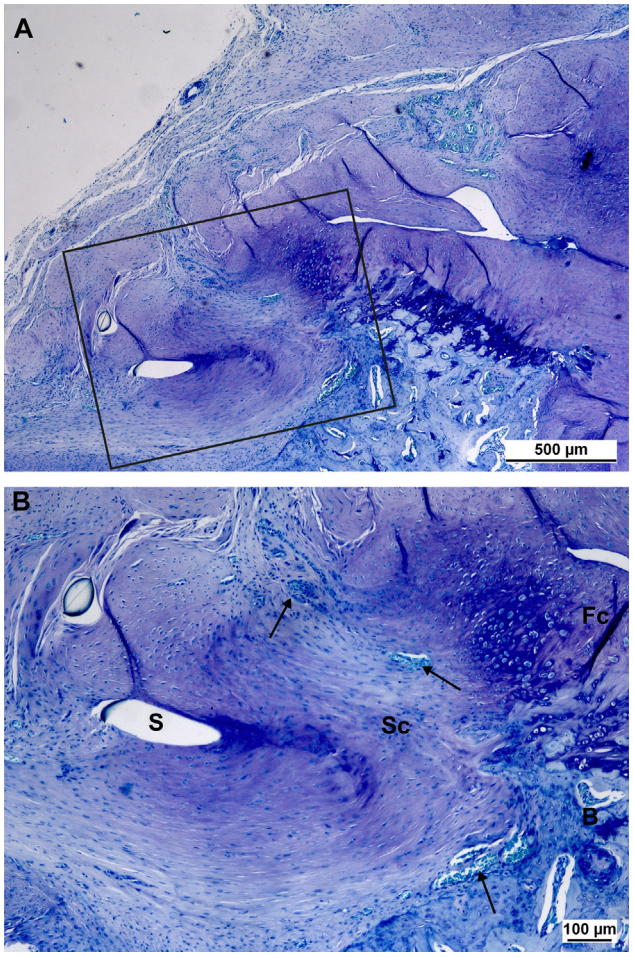

Fig. 2. A and B. Subsequent to a repair, there is an abnormal enthesis with inferior tissue quality (A, 500 µm). In detail (B, 100 µm), there is scar tissue (= SC) close to the bone (= B) with parts of the remaining suture (= S). Some rest of the remaining fibrocartilage is on the top left (= FC).

divided into four zones, namely tendon, unminerealized fibrocartilage, mineralized fibrocartilage and bone [41–44] (Fig. 1A and B). The ensuing scar tissue formation after RCTR (Fig. 2A and B) has a detrimental effect on the biomechanical characteristics of this area compared to the four zones of the physiological enthesis. Hence, there is a strong drive to investigate the role of potential molecular therapies in the form of biological augments that may restore the pathologic enthesis to a near normal physiological state.

4.1. Growth factors to augment the enthesis

Several growth factors have been shown to play an integral role in enthesis healing by regulating inflammation and matrix synthesis, as well as cell migration, proliferation and differentiation. The application of a single growth factor has been investigated in vitro and in several animal studies (e.g. BMP-12 [45] or TGFβ [46]). Single growth factor administration did not improve the functional or mechanical properties of the repair. Since the healing process is regulated by more than one growth factor [47], Rodeo et al. implanted TGFb1 to TGFb3, BMP 2 to BMP 7 and FGF applied into a collagen type I sponge in between the tendon and the footprint of a sheep rotator cuff repair healing site [48]. They reported improved biomechanical properties after 6 and 12 weeks with an improved bone and soft tissue volume compared to the control group, where only a surgical reconstruction was performed. When normalizing the tissue volume of the scar tissue to the normal physiological tendon size, no differences were seen with respect to maximal load to failure. Even though the growth factor cocktail accelerated healing, it did not change quality of repair. To date, there are no clinical studies in humans investigating the role of biological augments with RC reconstruction.

4.2. Using platelet concentrates to augment the enthesis

Many of the cytokines present during enthesis healing are also found in high concentrations in platelet concentrates (e.g. TGFβ1, PDGF, bFGF, VEGF, EGF, and IGF-1) [49–52]. Platelet concentrates have also been shown to promote neovascularization, which may increase blood supply enabling cells to migrate to the healing site. Since chronic RC tears show a rather unfavorable healing milieu, neovascularisation may be potentially therapeutic. This hypothesis is partly negated by one study, in which increased neovascularization after biological augmentation of RC tears using platelet concentrates did not lead to an improved clinical or radiographical outcome [53].

In contrast to the application of growth factors, autologous platelet concentrates are available without the risk associated with allogenic products and they can be prepared during RC reconstruction. Platelet concentrates have therefore been explored as a promising potential biologic augment for healing. Pre-clinical in vitro studies have shown promising results, but only a few large-scale clinical studies have investigated its benefit for the healing RC with inconclusive results.

Table 2
Platelet-rich concentrates can be divided into four categories depending on their leukocyte and fibrin content. Each group shows different characteristics. The most important ones are depicted in the table.

	Leucocyte count	Fibrin density	Injectable	Scaffold like density	Anticoagulants/gelifying agents added	Platelet concentrate brands	Concentration factor of platelets
L-PRP	High	Low	✓	✗	✓	Biomet GPSIII (Biomet, USA)	3–8 ×
P-PRP	Low	Low	✓	✗	✓	Vivostat (Vivostat A/S, Denmark)	3–9 ×
L-PRF	High	High	✗	✓	✗	Choucron	
P-PRF	Low	High	✗	✓	✓	Cascade (Cascade Medical, USA)	1–1.5 ×

The interpretation of the results of these studies is complicated by the fact that there are different platelet concentrates, with varying growth factor release patterns over time. Reasons for these different properties may be found in the lack of standardization between the different platelet concentration systems, with every system containing different concentration of factors and varied activation status of the platelets. Other reasons for inconsistencies between these systems may be due to the different concentrations of other bioactive ingredients such as leukocytes, red blood cells and the fibrinogen. For this reason, Dohan Ehrenfest et al. have divided the different platelet concentrates depending on their leukocyte and fibrin content into four categories [54] (Table 2):

- leucocyte- and platelet-rich plasma (L-PRP) (e.g. GPS III, Magellan and SmartPReP);
- pure platelet-rich plasma (P-PRP) (e.g. Vivostat PRF, ACP and cell separator PRP);
- leucocyte and platelet-rich fibrin (L-PRF) (e.g. L-PRF);
- pure platelet-rich fibrin (P-PRF) (e.g. Cascade FIBRINET PRFM system).

4.2.1. Leukocyte and platelet-rich plasma (L-PRP)

4.2.1.1. Full thickness RC tears. Several clinical studies have investigated the application of L-PRP to the RC reconstruction site. Randelli et al. [55] performed a RCTR in 53 subjects with 26 of these patients receiving L-PRP augmentation. In the control group ($n = 27$), the RC was reconstructed without a L-PRP treatment. In the first postoperative month, the L-PRP group showed decreased pain scores and after 3 months an increased simple shoulder test (SST). After 6, 12, and 24 months, no radiographical or clinical differences were reported. Another study, where large and massive RC tears were augmented using L-PRP also showed no benefit of the L-PRP augmentation except radiographically for smaller iterative tears in the L-PRP group seen in MRI scans [56]. However, the clinical outcome measured with the UCLA score, simple shoulder test score, constant score and strength was not different in the L-PRP and control group.

One explanation for these results may be the rather high platelet concentrations. The platelet concentrations in L-PRP is up to 4 times as higher than in physiological blood. There is evidence that platelet concentrations over 2.5-fold result in a reduction in cell proliferation and might therefore have a negative impact on healing [57]. Gumina et al. [58] therefore applied platelet-leukocyte membranes, that only allowed 1.7 times greater platelet counts compared to the physiological blood concentrations. They reported improved repair integrity in the L-PRP group compared to the control group, where only a conventional repair was performed ($P = 0.04$). However, they did not find any difference with respect to the clinical outcome [58].

In a recent study, Carr et al. investigated both the clinical and tissue effects of the coapplication of PRP injection with arthroscopic acromioplasty in patients with chronic rotator cuff tendinopathy. Patients were randomized to arthroscopic acromioplasty alone or in combination with an injection of autologous L-PRP into the subacromial bursa. The coapplication of L-PRP did not affect clinical outcomes. Of concern was the finding that L-PRP significantly alters the tissue characteristics in tendons after surgery, with reduced cellularity and vascularity, and increased levels of apoptosis with an increased expression of p53-positive apoptotic cells [59].

4.2.1.2. Partial thickness RC tears. In a prospective study, a single ultrasound-guided and intralesional injection of L-PRP resulted in significant sustained improvement of pain, function, and MRI outcomes in participants with refractory RC tears up to 1 year after injection [60]. This was confirmed by a study of one of the co-authors (AL) where they found a statistically significant and clinically relevant effect on RC tear size and clinical parameters after L-PRP infiltration [61].

4.2.2. Pure platelet-rich plasma (P-PRP)

4.2.2.1. Full thickness RC tears. In a recently published randomized and single blinded study, 48 patients were randomly assigned to receive either a P-PRP augmented (24 patients) or a conventional (24 patients) RC reconstruction after large or massive tears [62]. The authors used a leucoreduction plasmapheresis system for the production of P-PRP (COBE Spectra LRS Turb, Cardian BCT, Lakewood, Co, USA). The retear rate of the P-PRP group (20.0%) was significantly lower than that of the conventional group (55.6%) ($P = 0.023$). Clinical outcomes showed no statistical difference between the 2 groups (all $P > 0.05$) except for the overall function ($P = 0.043$). The change in the 1-year postoperative and immediately postoperative cross-sectional area (CSA) of the supraspinatus was significantly different between the 2 groups: $-15.54 \pm 94.34\ mm^2$ in the PRP group versus $-85.62 \pm 103.57\ mm^2$ in the conventional group ($P = .047$). A limitation of this study is the rather small sample size [62]. These promising results were confirmed in another recent cohort study [63].

In contrast, no differences were seen in the clinical outcome nor in the retear rate up to 24 months postoperatively using the Vivostat system [64]. Again, a limitation of this study is the rather small sample size. Similarly, no significant differences were found when applying autologous conditioned plasma (ACP, Arthrex, Naples, FL, USA) or platelet-rich plasma prepared by apharesis during RC reconstruction in two randomized controlled studies [65,66]. Another option of augmenting RC reconstruction is the postoperative injection of platelet concentrates. Autologous conditioned plasma (ACP, Arthrex, Naples, FL, USA) injected in an ultrasound-guided manner 7 and 14 days postoperative after RC reconstruction did not accelerate early tendon healing measured in MRI scans and functional recovery, measured in Quick DASH, Oxford Shoulder Score and VAS compared to a control group [67].

4.2.2.2. Partial thickness RC tears. Except for a case report [68], there is no study investigating the impact of P-PRP on the clinical and radiological outcome of partial thickness tears.

4.2.3. Leukocyte and platelet-rich fibrin (L-PRF)

4.2.3.1. Full thickness RC tears. In vitro studies showed more constant and longer growth factor release patterns in L-PRF compared to L-PRP and better migration properties of mesenchymal stem cells and entdothelial cells [51]. But to date, the clinical studies have not demonstrated any benefits with respect to the use of L-PRF. Zumstein et al. augmented the RC reconstruction in patients using L-PRF in a randomized controlled trial [53]. In the 10 patients, where L-PRF was added, an increased vascularization was reported six weeks postoperative ($P = 0.001$) when compared to a control group of patients ($n = 10$), which did not receive L-PRF. Clinical examinations including subjective shoulder value, visual analog scale, Constant and Simple Shoulder Test scores did not reveal significant differences 6 and 12 weeks postoperative. A limitation of this study is the rather small sample size. In a subsequent study, 35 patients were randomized to receive arthroscopic RC reconstruction with L-PRF locally applied to the repair site ($n = 17$) or without L-PRF ($n = 18$). They concluded that arthroscopic RC reconstruction with application of L-PRF yields no beneficial effect in clinical outcome, anatomic healing rate, mean postoperative defect size and tendon quality at 12 months of follow-up [2].

4.2.3.2. Partial thickness RC tears. L- PRF is not applicable in partial RC tears.

4.2.4. Pure platelet-rich fibrin (P-PRF)

4.2.4.1. Full thickness RC tears. Several authors did not show significant differences in clinical outcome and similar or worst radiographical outcome after application of PRFM (Cascade Autologous Platelet System, Musculoskeletal Transplant Foundation, Edison, NJ, USA) [69–71]. In a randomized controlled trial, Rodeo et al. [70] performed a RC reconstruction in 79 patients. The patients were randomized to either receive P-PRF at the tendon-bone interface ($n = 40$) or a standard repair with no P-PRF ($n = 39$). There were no differences in tendon-bone healing rate after 12 months (67% in the P-PRF group, 81% in the control group, $P = 0.2$), the manual muscle strength or the clinical outcome between the two groups. Interestingly, the platelet count had no effect on healing. Regression analysis suggested that P-PRF may have a negative effect on healing (odds ratio: 5.8), as it was a significant predictor for a tendon defect at 12 weeks. In another cohort study, similar results were found with a significantly higher retear rate in the PRFM group [15]. Castricini et al. [72] reported no significant difference when comparing the Constant Score ($P = 0.44$) and the rerupture rate (1 of 40 in the P-PRF group, 4/38 in the control group; $P = 0.07$) of the P-PRF and the control group. Also, no difference was found between both groups when comparing the tendon thickness ($P = 0.18$). However, their results are only applicable for small and medium RC tears.

4.2.4.2. Partial thickness RC tears. To our knowledge, there is no study investigating the impact of P-PRP on the clinical and radiological outcome of partial thickness tears.

In conclusion, the benefit of platelet concentrates in a clinical setting remains questionable when looking at the current evidence. In a meta-analysis of randomized controlled trials up to 2014, Li et. al. [73] concluded that platelet concentrates have no benefit with respect to retear rate and overall clinical outcomes for the arthroscopic RC reconstructions.

4.3. Cell-based augmentation

Cells are essential for the healing process of the RC tears. Tendons are relatively hypocellular. Furthermore, a study by Hernigou et al. [74] has revealed a massive reduction of mesenchymal stem cell levels of up to 70% in bone marrow harvested at the tendon-bone interface of patients with symptomatic RC tears compared with patients with an intact RC. The relative lack of cellular machinery in and around the RC enthesis coupled with poor vascularity results in poor healing potential following acute or overuse injuries [75]. In the recent years, biological augmentation using cell-based therapy has been investigated. The application of stem cells has shown promising results.

4.3.1. Stem cells to augment the enthesis

The application of stem cells to the healing site has significant potential as a future therapy. Stem cells can be classified according to their ability to differentiate into other cell types. They can be divided into (1) embryonic stem cells and (2) adult stem cells (Table 3). While totipotent embryonic stem cells from the first couple of cell division cycles can divide into every cell of an organism, pluripotent stem cells lack differentiation into extra-embryonic tissue like the placenta. In contrast, multipotent embryonic stem cells can only divide into a limited range of cells of a single tissue type. Adult stem cells, the second group of stem cells are multipotent undifferentiated cells found in adult tissue. They include adipose-derived stem cells (AD-MSC) and mesenchymal stem cells (MSCs). These cells replace the dying cells in the tissue. Placenta derived stem cells also belong to the adult stem cell group. Unlike MSCs and AD-MSCs, they are pluripotent and have therefore the capacity to differentiate toward all three germ layers [76].

Even though embryonic stem cells offer a wider therapeutic potential than adult stem cells, especially when using totipotent cells, their use in research is ethically controversial and an increased risk for teratoma development has been reported. When using adult stem cells, ethical issues are not as significant and malignant transformations are much less likely.

4.3.1.1. Application of mesenchymal stem cells in RCTR. There is evidence that MSCs may improve rotator cuff repair healing. The possibility to harvest bone marrow aspirate concentrate (BMAC) during RC reconstruction in a more or less standardized manner and the fact that BMAC apart from other cells and platelets, contains MSCs has made BMAC a promising option for a biological augmentation of the RCTR.

There is limited literature investigating the clinical effect of the biological augmentation using MSCs or BMAC to improve RC healing. In a study published in 2014, Hernigou et al. showed that arthroscopic RC reconstructions that were augmented with bone marrow derived MSCs showed a 13% retear rate 10 years postoperatively compared to 46% in the control group, that only received a RC single row repair without application of MSCs [77]. In another study [78], 14 patients with complete RC tears received a RC reconstruction with a subsequent injection of autologous bone marrow derived stem cells. The MRI analysis that was performed 12 months after surgery revealed good tendon integrity in all the subjects. Clinical findings remained unaltered in the following year in all but one patient, who relapsed into loss of strength and pain, and was considered as a bad result [78]. However, a limitation of this study was the absence of a control group and the rather small study population.

Several studies have investigated the isolation and characterization of MSCs harvested from different shoulder tissues. Mazzocca et al. [79] were able to harvest MSCs from the bone marrow through the anchor tunnel of the humeral head during arthroscopic RC reconstructions. These cells were then cultivated. Doing so, the authors were able to produce connective tissue progenitor cells, which have the potential of being used in future operations. In another study, MSCs that were harvested from the humerus were treated with a single physiologic dose of insulin [80]. The authors were able to show that these cells differentiated into cells with characteristics consistent with tendon [80]. The potential for MSCs to differentiate into tendon after a single dose of insulin may

Table 3
Scaffolds can be divided into three categories. This table shows the most popular commercially available scaffolds in each category.

Product (company, country)	Source	Tissue/type	Cross-linking	Available size (cm)	Sterilization	Comments
Xenografts						
CuffPatch (Arthrotek, USA)	Porcine	Small intestine submucosa	Yes	6.5 × 9	Gamma irradiation	Acellular
Connexa (Tornier, Wright Medical, USA)	Porcine	Dermis	No	2 × 4 up to 5 × 10	Patented technique	Acellular
Zimmer collagen repair patch (Zimmer, USA)	Porcine	Dermis	Yes	5 × 10	Gamma irradiation	Acellular
Restore (DePuy Orthopedics, USA)	Porcine	Small intestine submucosa	No	2 × 6	E-beam	Acellular
TissueMend (Stryker Orthopedics, USA)	Foetal bovine	Dermis	No	5 × 6	Gamma irradiation	Acellular
Allografts						
Allopatch HD (MTF, USA)	Human	Dermis	No	Multiple	Aseptic technique	Acellular
ArthroFlex (Arthrex, USA)	Human	Dermis	No	Multiple	Patented technique	Acellular
Dermaspan (Zimmer Biomet, USA)	Human	Dermis	No	5 × 5 up to 5 × 10	Patented technique	Acellular
GraftJacket (Wright Medical, USA)	Human	Dermis	No	2 × 4 up to 5 × 10	Aseptic technique	Acellular
Synthetic grafts						
Artelon (Artimplant AB, Sweden)	Knitted mesh	Polyurethane urea polymer	N.A.	3 × 4 up to 6 × 9	Sterile	Degradable
Gore-Tex patch WL (Gore & Associates, USA)	Synthetic	ePTFE	N.A.	5 × 10 up to 26 × 34	Sterile	Non-degradable
Lars ligament (Lars, France)	Synthetic	Terephthalic polyethylene polyester	N.A.	Multiple	Sterile	Non-degradable
Poly-tape (Xiros Ltd, Neoligaments, UK)	Synthetic	Polyester ethylene terephthalate	N.A.	Up to 5 × 80	Sterile	Non-degradable
X-repair (Synthasome, USA)	Multilayer woven mesh	Poly-l-lactic acid	N.A.	Up to 4 × 4.3	Sterile	Degradable

assist in developing practical biologic options for augmentation of RC reconstructions. Another group characterized MSCs from four different shoulder tissues (synovium of the glenohumeral joint, subacromial bursa, margin of the ruptured supraspinatus tendon and residual tendon stump on the greater tuberosity) in 19 patients [81]. The subacromial tissue showed more passage 0 cells and these cells kept their proliferative ability for more passages. They also showed a higher osteogenic and adipogenic potential. But the chondrogenic potential in subacromial MSCs was lower in comparison to the MSCs harvested from the enthesis. An interpretation of these in vitro results is difficult and the conclusion made by the authors was that subacromial bursa MSC's are a good candidate for the source of MSCs in RC reconstructions. But this is questionable. Not a high adipogenic, but a chondrogenic potential would be desirable for the healing of the enthesis since two out of the four physiological zones in the RC enthesis consist of fibrocartilage. But this very chondrogenic potential is rather low in the subacromial bursa MSCs.

4.3.1.2. Application of adipose-derived stem cells in RC reconstructions. Another source of MSCs is the fatty tissue. Adipose derived stem cells (AD-MSCs) can be harvested via relatively minimally invasive liposuction. When compared to bone marrow derived stem cells, they show a similar morphology, and CD surface marker protein expression, but a higher colony-forming and adipogenic potential [82]. When injected into a chronic RC healing model in a rabbit, AD-MSCs increased the maximal load to failure compared to the control group where only saline was injected into the repair site [83]. However, this difference was not statistically significant. Significantly better tendon architecture, decreased inflammatory cell numbers and significantly increased tensile strength were found, when human AD-MSCs were injected into a rat RC tendinopathy model [84]. In contrast, the application of ASCs in a rat RC reconstruction model did not improve the biomechanical properties of the tendon-to-bone healing in another study [85]. Due to the contradicting literature, it is unclear if AD-MSCs represents a good alternative to increase the tendon-bone healing in the RC tear in humans. More animal and human clinical studies will be necessary to prove its benefit in RC healing.

4.3.1.3. Application of placental derived stem cells in RC reconstructions. In the recent years, placental human derived MSCs gained attention in orthopaedic research. Placental human derived MSCs can be isolated and expanded relatively easy and have shown to have multilineage differentiation potential similar to MSCs derived from bone marrow [86]. In a rat patellar tendinopathy model, the application of placenta derived stem cells has shown better biomechanical, as well as better histomorphological results [87]. This makes these cells attractive for the biological augmentation of the RC reconstructions. Further in vitro and future clinical studies will be necessary to explore their safety and potential in RC healing.

4.4. Scaffold based augmentation

The application of scaffolds is another promising way of augmenting RC reconstruction sites, especially when dealing with large and complex RC tears. Even though a scaffold interposition may help bridging rotator cuff tendon defects, it does not address the issues related to RC retraction, namely the reduced irreversible biomechanical properties of the rotator cuff muscle. The use of interposition scaffolds in rotator cuff repair is therefore questionable. On the other hand, scaffolds with which the tendon is augmented not only may increase the initial strength of the reconstruction and allow gradual tissue ingrowth, but also protect the healing tissue. Three different types of scaffolds exist (Table 4):

- xenografts (graft transferred from another species);
- allografts (graft from an individual to another of the same species);
- synthetic grafts.

While xenografts and allografts are postulated to provide a structural environment that may improve healing as well as remodeling, synthetic grafts lack this feature. But, the mechanical strength of synthetic grafts may help to stabilize the repair until the tissue

Table 4
Classification and characteristics of stem cells.

	Embryonic stem cells	Adult stem cells	
		Mesenchymal stem cells (MSC)	Placenta derived stem cells
Source	From inner cell mass of blastocyst	From different tissues of the mature body (e.g. bone marrow, fat)	From the placenta ("young MSCs")
Potentcy	Toti- to pluripotent Give rise to all cell types (except placenta	Multipotent Give rise to a limited number of cell types (MSC: chondrocytes, osteocytes, adipocytes)	Pluripotent May give rise to much more cell types than MSC
Self renewal	Long-term self renewal ("immortal")	Limited self renewal	Limited self renewal
Availability	Readily available Blastocysts not used for in vitro Retilization are readily available	Some availability Difficult to extract from tissue in big numbers	Readily available
Immune rejection	Possible With somatic cell nuclear transfer not an issue	Unlikely Patients are using their own patients	Unlikely
Ethical issues	Major	None	Minor
Teratoma formation	Increased risk	No teratoma formation	No teratoma formation

is strong enough again to transmit the muscle load to the humeral head.

4.4.1. Using xenografts to augment the enthesis

Extra-cellular matrix patches are scaffold devices designed to create a cellular reaction that leads to an inflammatory response, host cell infiltration and tendon-like remodeling. Even though the augmentation using porcine small intestine submucosa has shown to improve the histological healing properties (e.g. tendon-like remodeling) in several animal studies [88–90] and clinical studies, where large to massive chronic RC tears were augmented using a similar scaffold (Restore Orthobiologic Implant, DePuy Orthopaedics, Warsaw, IN, USA) showed no differences in the clinical outcome when compared to a control group [91]. Another group reported that 4 out of 19 (21%) patients treated with the same xenograft had a severe postoperative inflammatory reaction, which made a reoperation with a debridement and removal of the graft necessary. Since all the intra-operative cultures were negative, this reaction was most likely caused by the xenograft itself. Furthermore, no clinical benefit could be shown after a 2-year follow-up [92].

Inconsistent results were reported when using permacol (Zimmer Collagen Repair Patch, Zimmer Inc., Warsaw, IN, USA), an acellular porcine dermal collagen matrix. It is cross-linked and thus not susceptible to enzymatic degradation. Badhe et al. [93] reported good results 4.5 years after augmenting massive RCT in 10 patients with an intact repair in eight, and a retear in only two patients. On the other hand, Soler et al. [94] were using permacol as a bridging device. All of the four reconstructions failed within six months postoperatively and had signs of inflammation. No differences were seen when using extracellular matrix scaffolds in open RC revision surgery [95].

More promising results were reported in a study of 9 patients with massive, otherwise unrepairable RC tears, that have received a porcine dermal collagen patch augmentation. After a minimum follow-up of 2.5 years, all cases showed complete functional recovery as well as covering of the humeral head [96]. Another prospective comparative study showed a reduction of the retear rate and improved clinical outcome scores after ECM augmentation of arthroscopic repairs of large to massive RC tears [97].

4.4.2. Using allografts to augment the enthesis

When using GraftJacket allograft acellular human dermal matrix for the augmentation of large to massive RC tears, good results were reported [98,99]. In a prospective and randomized study, an arthroscopic RC reconstruction of tears larger than 3 cm was performed with either a GraftJacket augmentation ($n = 20$) or without augmentation ($n = 22$) [98] After a follow-up of 12 to 24 months (mean 14.5 months), significantly more intact repairs were found in the GraftJacket group (85%) compared to the control group (40%). American Shoulder and Elbow Surgeons and Constant scores in the GraftJacket group were statistically better at last follow-up.

4.4.3. Using synthetic scaffolds to augment the enthesis

Synthetic patch augmentation has shown to protect the repair site and reduce friction in the subacromial space. Ciampi et al. [100] were able to show, in a cohort of 152 patients with posterosuperior RC tears, a significant decrease in retear rate of 17% in the polypropylene patch augmentation group compared to 51% in the repair-only group at 1-year follow-up, as well as increased abduction strength and elevation at 3-year follow-up. In a recent study, poly-l-lactic acid bioabsorbable patches designed specifically to reinforce the surgical repair of tendons supported successful repair of large to massive RCT in 83% of patients at 12 months after surgery and 78% of patients at 42 months after surgery, with substantial functional improvement [101]. Promising results were also reported when using a bi-layered, absorbable reinforced poly (4)-hydroxybutyrate scaffold that can be used to reinforce RC reconstruction [102]. Augmenting the RC tears using this scaffold lead to improved repair integrity of 96% in 50 patients at the 6-month follow-up with no additional failure at the 1-year follow-up.

Another interesting approach is the combination of a synthetic patch with an autologous long head of the biceps tendon interposition in irreparable RC tears. A study in 60 patients showed a retear rate at 12 months follow-up of 15% compared to 40% in the control group [103]. It is unclear though, if the synthetic patch, the long head of the biceps tendon or the combination of the two lead to the improved retear rate.

5. Is it possible to augment the rotator cuff muscle?

RC tears have reportedly been associated with muscle atrophy, retraction and fatty infiltration. These changes have been found to be one of the main causes for a poor outcome after RC reconstruction. In the recent years, researchers have also focused on preventing and reversing these muscular changes.

5.1. Platelet concentrates to augment the rotator cuff muscle

There is evidence in the literature that the application of platelet concentrates may have a positive effect on muscle healing [104], improved pain relief [105], as well as a quicker return to sport [105,106]. Others reported no differences with respect to time to return to sport or re-injury rate 1 year after injecting a platelet

concentrate into the hamstrings after acute hamstring injuries. In all the above studies, acute muscle injuries were treated with platelet concentrate injections. As the mechanism of muscle injury after RC tendon tear is different from an acute muscle injury, it is questionable to what extent these results can be transferred to a chronic RC tear muscle model. Whether platelet-rich concentrates improve muscle quality after RC tear is unclear and not reported in the literature.

5.2. Cells to augment the rotator cuff muscle

In an animal study, Oh et al. [83] tenotomised the subscapularis muscle in rabbits. Six weeks postoperatively, they performed a tendon repair and injected adipose derived stromal cells (AD-MSC) into the subscapularis muscle. A second group, which received saline instead of AD-MSCs, served as a control group. The AD-MSC group showed a significantly larger compound muscle action potential area than the control group ($P = 0.029$) and a higher load-to-failure (AD-MSC group: 87.02 ± 29.81 N versus saline group: 59.85 ± 37.77 N, $P = 0.085$). Furthermore, subscapularis muscles, in which AD-MSCs were injected showed less fatty infiltration with a fat content of only $29 \pm 15\%$ compared to $43 \pm 9\%$ in the control group [83]. To our knowledge, no clinical studies exist that investigate the benefit of cells for the augmentation of the RC muscle after reconstruction.

5.2.1. Drugs that may augment rotator cuff muscle

Poly (ADP-ribose) 4 polymerase-1 (PARP-1) has been shown to be a key regulator of inflammation, apoptosis, muscle atrophy, muscle regeneration as well as adipocyte development. In PARP-1 knock-out (PARP-1 KO) mice, our team [2] performed a combined tenotomy of the supra- and infraspinatus muscle and found significant less muscle retraction ($P = 0.008$) and less fatty infiltration ($P = 0.028$) after 12 weeks and a significant decrease in the expression of inflammatory, apoptotic, adipogenic and muscular atrophy genes at both the 1 week and 6 weeks time points in the PARP-1 KO group compared to the WT group. The PARP-1 KO group also showed a significant decrease in the expression of inflammatory, apoptotic, adipogenic and muscular atrophy genes at both the 1 week and 6 weeks time points. Therefore, PARP-1 is not only a key regulator of muscular deterioration, but may also be an interesting target to improve muscular properties after RC tear and repair using a PARP-1 inhibitor.

The application of nandrolone decanoate, an anabolic steroid has shown to not only prevent muscle atrophy but also fatty infiltration in animal models making this drug an interesting treatment option for the prevention of RC muscle degeneration after RC tear [107]. It has been proposed that vitamin D blood levels negatively correlate with fatty infiltration after RC tear and positively correlate with muscle torque in the same patients [108]. This suggests that a vitamin D supplementation would have a positive impact on muscular changes after RC tears and repairs. However in a clinical study, there was no correlation between rotator cuff healing and vitamin D blood levels [40].

6. Conclusion

Due to the high retear rate after RC reconstruction, there is a great interest in it's biological augmentation. Even though cytokines have shown the potential to improve the RC 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. Further studies are necessary to identify the right combination, timing and concentration of the cytokines.

Tendinopathies and partial-thickness tears may be interesting targets for the biological augmentation of the rotator cuff. Yet, we must be aware that animal studies have shown that, instead of a physiological enthesis, an abundance of scar tissue is formed.

Using stem cells to biologically augment the RC reconstruction might have a great potential since these cells can be differentiated into different cell types that are important for the healing process. However, further studies are necessary to understand how to control these stem cells in a safe and efficient way. Finally, much basic research is required to overcome the problems associated with using grafts as well as developing new drugs for the augmentation of RC reconstruction.

Disclosure of interest

Dr. Zumstein is a consultant for Medacta International and Angiocrine Biosciences. Dr Lädermann, Dr. Raniga and Dr. Schär declare that they have no competing interest.

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References

[1] Galatz LM, Ball CM, Teefey SA, Middleton WD, Yamaguchi K. The outcome and repair integrity of completely arthroscopically repaired large and massive rotator cuff tears. J Bone Joint Surg Am 2004;86-A(2):219–24.
[2] Kuenzler M, Nuss KM, Karol A, Schaer M, Hottiger MO, Raniga S, et al. Neer Award 2016: reduced muscle degeneration and decreased fatty infiltration after rotator cuff tear in a PARP-1 knock-out mouse model. In: ASES., editor. ASES Speciality Day March 2016. Orlando: FL: ASES; 2016.
[3] Meyer DC, Farshad M, Amacker NA, Gerber C, Wieser K. Quantitative analysis of muscle and tendon retraction in chronic rotator cuff tears. Am J Sports Med 2012;40:606–10.
[4] Adler RS, Fealy S, Rudzki JR, Kadrmas W, Verma NN, Pearle A, et al. Rotator cuff in asymptomatic volunteers: contrast-enhanced US depiction of intratendinous and peritendinous vascularity. Radiology 2008;248(3):954–61.
[5] Lohr JF, Uhthoff HK. The microvascular pattern of the supraspinatus tendon. Clin Orthop Relat Res 1990;(254):35–8.
[6] Matthews TJ, Smith SR, Peach CA, Rees JL, Urban JP, Carr AJ. In vivo measurement of tissue metabolism in tendons of the rotator cuff: implications for surgical management. J Bone Joint Surg Br 2007;89(5):633–8.
[7] Rathbun JB, Macnab I. The microvascular pattern of the rotator cuff. J Bone Joint Surg Br 1970;52(3):540–53.
[8] Rothman RH, Parke WW. The vascular anatomy of the rotator cuff. Clin Orthop Relat Res 1965;41:176–86.
[9] Lundgreen K, Lian OB, Engebretsen L, Scott A. Tenocyte apoptosis in the torn rotator cuff: a primary or secondary pathological event? Br J Sports Med 2011;45(13):1035–9.
[10] Millar NL, Hueber AJ, Reilly JH, Xu Y, Fazzi UG, Murrell GA, et al. Inflammation is present in early human tendinopathy. Am J Sports Med 2010;38:2085–91.
[11] Gerber C, Meyer D, Frey E, von Rechenberg B, Hoppeler H, Frigg R, et al. Neer Award 2007: reversion of structural muscle changes caused by chronic rotator cuff tears using continuous musculotendinous traction. An experimental study in sheep. J Shoulder Elbow Surg 2009;18:163–71.
[12] Schmutz S, Fuchs T, Regenfelder F, Steinmann P, Zumstein M, Fuchs B. Expression of atrophy mRNA relates to tendon tear size in supraspinatus muscle. Clin Orthop Relat Res 2009;467(2):457–64.
[13] Frey E, Regenfelder F, Sussmann P, Zumstein M, Gerber C, Born W, et al. Adipogenic and myogenic gene expression in rotator cuff muscle of the sheep after tendon tear. J Orthop Res 2009;27(4):504–9.
[14] Barry JJ, Lansdown DA, Cheung S, Feeley BT, Ma CB. The relationship between tear severity, fatty infiltration, and muscle atrophy in the supraspinatus. J Shoulder Elbow Surg 2013;22(1):18–25.
[15] Angeline ME, Rodeo SA. Biologics in the management of rotator cuff surgery. Clin Sports Med 2012;31(4):645–63.
[16] Andrianjafiniony T, Dupre-Aucouturier S, Letexier D, Couchoux H, Desplanches D. Oxidative stress, apoptosis and proteolysis in skeletal muscle repair after unloading. Am J Physiol Cell Physiol 2010;299(2):C307–15.
[17] Benson RT, McDonnell SM, Knowles HJ, Rees JL, Carr AJ, Hulley PA. Tendinopathy and tears of the rotator cuff are associated with hypoxia and apoptosis. J Bone Joint Surg Br 2010;92(3):448–53.
[18] Millar NL, Wei AQ, Molloy TJ, Bonar F, Murrell GA. Cytokines and apoptosis in supraspinatus tendinopathy. J Bone Joint Surg Br 2009;91:417–24.
[19] Sishi BJ, Engelbrecht AM. Tumor necrosis factor alpha (TNF-alpha) inactivates the PI3-kinase/PKB pathway and induces atrophy and apoptosis in L6 myotubes. Cytokine 2011;54(2):173–84.

[20] Arnold L, Henry A, Poron F, Baba-Amer Y, van Rooijen N, Plonquet A, et al. Inflammatory monocytes recruited after skeletal muscle injury switch into anti-inflammatory macrophages to support myogenesis. J Exp Med 2007;204(5):1057–69.
[21] Murphy PG, Loitz BJ, Frank CB, Hart DA. Influence of exogenous growth factors on the synthesis and secretion of collagen types I and III by explants of normal and healing rabbit ligaments. Biochem Cell Biol 1994;72(9–10):403–9.
[22] Zanou N, Gailly P. Skeletal muscle hypertrophy regeneration: interplay between the myogenic regulatory factors (MRFs) insulin-like growth factors (IGFs) pathways. Cell Mol Life Sci 2013;70(21):4117–30.
[23] Hays PL, Kawamura S, Deng XH, Dagher E, Mithoefer K, Ying L, et al. The role of macrophages in early healing of a tendon graft in a bone tunnel. J Bone Joint Surg Am 2008;90(3):565–79.
[24] Bishop J, Klepps S, Lo IK, Bird J, Gladstone JN, Flatow EL. Cuff integrity after arthroscopic versus open rotator cuff repair: a prospective study. J Shoulder Elbow Surg 2006;15(3):290–9.
[25] Boileau P. Arthroscopic repair of full-thickness tears of the supraspinatus: does the tendon really heal? J Bone Joint Surg Am 2005;87(6):1229–40.
[26] Charousset C, Bellaiche L, Kalra K, Petrover D. Arthroscopic repair of full-thickness rotator cuff tears: is there tendon healing in patients aged 65 years or older? Arthroscopy 2010;26(3):302–9.
[27] Cho NS, Rhee YG. The factors affecting the clinical outcome and integrity of arthroscopically repaired rotator cuff tears of the shoulder. Clin Orthop Surg 2009;1(2):96–104.
[28] Nho SJ, Shindle MK, Adler RS, Warren RF, Altchek DW, MacGillivray JD. Prospective analysis of arthroscopic rotator cuff repair: subgroup analysis. J Shoulder Elbow Surg 2009;18(5):697–704.
[29] Oh JH, Kim SH, Kang JY, Oh CH, Gong HS. Effect of age on functional and structural outcome after rotator cuff repair. Am J Sports Med 2010;38(4):672–8.
[30] Grondel RJ, Savoie 3rd FH, Field LD. Rotator cuff repairs in patients 62 years of age or older. J Shoulder Elbow Surg 2001;10(2):97–9.
[31] Worland RL, Arredondo J, Angles F, Lopez-Jimenez F. Repair of massive rotator cuff tears in patients older than 70 years. J Shoulder Elbow Surg 1999;8(1):26–30.
[32] Galatz LM, Silva MJ, Rothermich SY, Zaegel MA, Havlioglu N, Thomopoulos S. Nicotine delays tendon-to-bone healing in a rat shoulder model. J Bone Joint Surg Am 2006;88(9):2027–34.
[33] Baumgarten KM, Gerlach D, Galatz LM, Teefey SA, Middleton WD, Ditsios K, et al. Cigarette smoking increases the risk for rotator cuff tears. Clin Orthop Relat R 2010;468(6):1534–41.
[34] Bedi A, Fox AJ, Harris PE, Deng XH, Ying L, Warren RF, et al. Diabetes mellitus impairs tendon-bone healing after rotator cuff repair. J Shoulder Elbow Surg 2010;19(7):978–88.
[35] Chen AL, Shapiro JA, Ahn AK, Zuckerman JD, Cuomo F. Rotator cuff repair in patients with type I diabetes mellitus. J Shoulder Elbow Surg 2003;12(5):416–21.
[36] Cohen DB, Kawamura S, Ehteshami JR, Rodeo SA. Indomethacin celecoxib impair rotator cuff tendon-to-bone healing. Am J Sports Med 2006;34(3):362–9.
[37] Chan KM, Fu SC. Anti-inflammatory management for tendon injuries: friends or foes? Sports Med Arthrosc Rehabil Therap Technol 2009;1(1):23.
[38] Tilley BJ, Cook JL, Docking SI, Gaida JE. Is higher serum cholesterol associated with altered tendon structure or tendon pain? A systematic review. Br J Sports Med 2015;49(23):1504–9.
[39] Angeline ME, Ma R, Pascual-Garrido C, Voigt C, Deng XH, Warren RF, et al. Effect of diet-induced vitamin D deficiency on rotator cuff healing in a rat model. Am J Sports Med 2014;42:27–34.
[40] Ryu KJ, Kim BH, Lee Y, Dan J, Kim JH. Low serum vitamin D is not correlated with the severity of a rotator cuff tear or retear after arthroscopic repair. Am J Sports Med 2015;43(7):1743–50.
[41] Galatz LM, Sandell LJ, Rothermich SY, Das R, Mastny A, Havlioglu N, et al. Characteristics of the rat supraspinatus tendon during tendon-to-bone healing after acute injury. J Orthop Res 2006;24(3):541–50.
[42] Gerber C, Schneeberger AG, Perren SM, Nyffeler RW. Experimental rotator cuff repair. A preliminary study. J Bone Joint Surg Am 1999;81(9):1281–90.
[43] Thomopoulos S, Hattersley G, Rosen V, Mertens M, Galatz L, Williams GR, et al. The localized expression of extracellular matrix components in healing tendon insertion sites: an in situ hybridization study. J Orthop Res 2002;20:454–63.
[44] Woo SL, Hildebrand K, Watanabe N, Fenwick JA, Papageorgiou CD, Wang JH. Tissue engineering of ligament and tendon healing. Clin Orthop Relat Res 1999;(Suppl. 367):S312–23.
[45] Seeherman HJ, Archambault JM, Rodeo SA, Turner AS, Zekas L, D'Augusta D, et al. rhBMP-12 accelerates healing of rotator cuff repairs in a sheep model. J Bone Joint Surg Am 2008;90(10):2206–19.
[46] Manning CN, Kim HM, Sakiyama-Elbert S, Galatz LM, Havlioglu N, Thomopoulos S. Sustained delivery of transforming growth factor beta three enhances tendon-to-bone healing in a rat model. J Orthop Res 2011;29(7):1099–105.
[47] Wurgler-Hauri CC, Dourte LM, Baradet TC, Williams GR, Soslowsky LJ. Temporal expression of 8 growth factors in tendon-to-bone healing in a rat supraspinatus model. J Shoulder Elbow Surg 2007;16(5 (Suppl. 1)):S198.
[48] Rodeo SA, Potter HG, Kawamura S, Turner AS, Kim HJ, Atkinson BL. Biologic augmentation of rotator cuff tendon-healing with use of a mixture of osteoinductive growth factors. J Bone Joint Surg Am 2007;89(11):2485–97.
[49] Boswell SG, Cole BJ, Sundman EA, Karas V, Fortier LA. Platelet-rich plasma: a milieu of bioactive factors. Arthroscopy 2012;28(3):429–39.
[50] Foster TE, Puskas BL, Mandelbaum BR, Gerhardt MB, Rodeo SA. Platelet-rich plasma: from basic science to clinical applications. Am J Sports Med 2009;37(11):2259–72.
[51] Schar MO, Diaz-Romero J, Kohl S, Zumstein MA, Nesic D. Platelet-rich concentrates differentially release growth factors induce cell migration in vitro. Clin Orthop Relat R 2015;473(5):1635–43.
[52] Zumstein MA, Berger S, Schober M, Boileau P, Nyffeler RW, Horn M, et al. Leukocyte- and platelet-rich fibrin (L-PRF) for long-term delivery of growth factor in rotator cuff repair: review, preliminary results and future directions. Curr Pharm Biotechnol 2012;13(7):1196–206.
[53] Zumstein MA, Rumian A, Lesbats V, Schaer M, Boileau P. Increased vascularization during early healing after biologic augmentation in repair of chronic rotator cuff tears using autologous leukocyte- and platelet-rich fibrin (L-PRF): a prospective randomized controlled pilot trial. J Shoulder Elbow Surg 2014;23(1):3–12.
[54] Dohan Ehrenfest DM, Rasmusson L, Albrektsson T. Classification of platelet concentrates: from pure platelet-rich plasma (P-PRP) to leucocyte- and platelet-rich fibrin (L-PRF). Trends Biotechnol 2009;27(3):158–67.
[55] Randelli P, Arrigoni P, Ragone V, Aliprandi A, Cabitza P. Platelet-rich plasma in arthroscopic rotator cuff repair: a prospective RCT study 2-year follow-up. J Shoulder Elbow Surg 2011;20(4):518–28.
[56] Charousset C, Zaoui A, Bellaiche L, Piterman M. Does autologous leukocyte-platelet-rich plasma improve tendon healing in arthroscopic repair of large or massive rotator cuff tears? Arthroscopy 2014;30(4):428–35.
[57] Graziani F, Ivanovski S, Cei S, Ducci F, Tonetti M, Gabriele M. The in vitro effect of different PRP concentrations on osteoblasts and fibroblasts. Clinical oral implants research 2006;17(2):212–9.
[58] Gumina S, Campagna V, Ferrazza G, Giannicola G, Fratalocchi F, Milani A, et al. Use of platelet-leukocyte membrane in arthroscopic repair of large rotator cuff tears: a prospective randomized study. J Bone Joint Surg Am 2012;94(15):1345–52.
[59] Carr AJ, Murphy R, Dakin SG, Rombach I, Wheway K, Watkins B, et al. Platelet-rich plasma injection with arthroscopic acromioplasty for chronic rotator cuff tendinopathy: a randomized controlled trial. Am J Sports Med 2015.
[60] Scarpone M, Rabago D, Snell E, Demeo P, Ruppert K, Pritchard P, et al. Effectiveness of platelet-rich plasma injection for rotator cuff tendinopathy: a prospective open-label study. Global Adv Health Med 2013;2(2):26–31.
[61] Lädermann A, Zumstein M, Kolo F, Grosclaude M, Koglin L, Schwitzguebel A. In vivo clinical radiological effects of platelet-rich plasma on interstitial supraspinatus lesion: case series. Orthop Traumatol Surg Res 2016 [In press].
[62] Jo CH, Shin JS, Lee YG, Shin WH, Kim H, Lee SY, et al. Platelet-rich plasma for arthroscopic repair of large to massive rotator cuff tears: a randomized, single-blind, parallel-group trial. Am J Sports Med 2013;41(10):2240–8.
[63] Jo CH, Shin JS, Shin WH, Lee SY, Yoon KS, Shin S. Platelet-rich plasma for arthroscopic repair of medium to large rotator cuff tears: a randomized controlled trial. Am J Sports Med 2015;43(9):2102–10.
[64] Antuna S, Barco R, Martinez Diez JM, Sanchez Marquez JM. Platelet-rich fibrin in arthroscopic repair of massive rotator cuff tears: a prospective randomized pilot clinical trial. Acta orthopaedica Belgica 2013;79(1):25–30.
[65] Malavolta EA, Gracitelli ME, Ferreira Neto AA, Assuncao JH, Bordalo-Rodrigues M, de Camargo OP. Platelet-rich plasma in rotator cuff repair: a prospective randomized study. Am J Sports Med 2014;42(10):2446–54.
[66] Werthel JD, Pelissier A, Massin P, Boyer P, Valenti P. Arthroscopic double row cuff repair with suture-bridging and autologous conditioned plasma injection: functional and structural results. Int J Shoulder Surg 2014;8(4):101–6.
[67] Wang A, McCann P, Colliver J, Koh E, Ackland T, Joss B, et al. Do postoperative platelet-rich plasma injections accelerate early tendon healing functional recovery after arthroscopic supraspinatus repair? A randomized controlled trial. Am J Sports Med 2015;43(6):1430–7.
[68] Freitag J, Lenssen R, Slimmon D, Balster S. The effect of platelet-rich plasma injections in the non-surgical treatment of a partial rotator cuff tear. Int J Case Rep Images 2014;5(7):524–30.
[69] Bergeson AG, Tashjian RZ, Greis PE, Crim J, Stoddard GJ, Burks RT. Effects of platelet-rich fibrin matrix on repair integrity of at-risk rotator cuff tears. Am J Sports Med 2012;40(2):286–93.
[70] Rodeo SA, Delos D, Williams RJ, Adler RS, Pearle A, Warren RF. The effect of platelet-rich fibrin matrix on rotator cuff tendon healing: a prospective and randomized clinical study. Am J Sports Med 2012;40(6):1234–41.
[71] Weber SC, Kauffman JI, Parise C, Weber SJ, Katz SD. Platelet-rich fibrin matrix in the management of arthroscopic repair of the rotator cuff: a prospective, randomized and double-blinded study. Am J Sports Med 2013;41(2):263–70.
[72] Castricini R, Longo UG, De Benedetto M, Panfoli N, Pirani P, Zini R, et al. Platelet-rich plasma augmentation for arthroscopic rotator cuff repair: a randomized controlled trial. Am J Sports Med 2011;39(2):258–65.
[73] Li X, Xu CP, Hou YL, Song JQ, Cui Z, Yu B. Are platelet concentrates an ideal biomaterial for arthroscopic rotator cuff repair? A meta-analysis of randomized controlled trials. Arthroscopy 2014;30(11):1483–90.
[74] Hernigou P, Merouse G, Duffiet P, Chevalier N, Rouard H. Reduced levels of mesenchymal stem cells at the tendon-bone interface tuberosity in patients with symptomatic rotator cuff tear. Int Orthop 2015;39(6):1219–25.
[75] Young M. Stem cell applications in tendon disorders: a clinical perspective. Stem Cells Int 2012;2012:637836.
[76] Miao Z, Jin J, Chen L, Zhu J, Huang W, Zhao J, et al. Isolation of mesenchymal stem cells from human placenta: comparison with human bone marrow mesenchymal stem cells. Cell Biol Int 2006;30(9):681–7.

[77] Hernigou P, Flouzat Lachaniette CH, Delambre J, Zilber S, Duffiet P, Chevallier N, et al. Biologic augmentation of rotator cuff repair with mesenchymal stem cells during arthroscopy improves healing and prevents further tears: a case-controlled study. Int Orthop 2014;38(9):1811–8.
[78] Ellera Gomes JL, da Silva RC, Silla LM, Abreu MR, Pellanda R. Conventional rotator cuff repair complemented by the aid of mononuclear. Knee Surg Sports Traumatol Arthrosc 2012;20(2):373–7.
[79] Mazzocca AD, McCarthy MB, Chowaniec DM, Cote MP, Arciero RA, Drissi H. Rapid isolation of human stem cells (connective tissue progenitor cells) from the. Am J Sports Med 2010;38(7):1438–47.
[80] Mazzocca AD, McCarthy MB, Chowaniec D, Cote MP, Judson CH, Apostolakos J, et al. Bone marrow-derived mesenchymal stem cells obtained during arthroscopic rotator cuff repair surgery show potential for tendon cell differentiation after treatment with insulin. Arthroscopy 2011;27(11):1459–71.
[81] Utsunomiya H, Uchida S, Sekiya I, Sakai A, Moridera K, Nakamura T. Isolation and characterization of human mesenchymal stem cells derived from shoulder tissues involved in rotator cuff tears. Am J Sports Med 2013;41(3):657–68.
[82] Vishnubalaji R, Al-Nbaheen M, Kadalmani B, Aldahmash A, Ramesh T. Comparative investigation of the differentiation capability of bone-marrow- and adipose-derived mesenchymal stem cells by qualitative and quantitative analysis. Cell Tissue Res 2012;347(2):419–27.
[83] Oh JH, Song BW, Lee YS. Measurement of volumetric bone mineral density in proximal humerus using quantitative computed tomography in patients with unilateral rotator cuff tear. J Shoulder Elbow Surg 2013.
[84] Chen HS, Su YT, Chan TM, Su YJ, Syu WS, Harn HJ, et al. Human adipose-derived stem cells accelerate the restoration of tensile strength of tendon and alleviate the progression of rotator cuff injury in a rat model. Cell Transplant 2015;24(3):509–20.
[85] Valencia Mora M, Antuna Antuna S, Garcia Arranz M, Carrascal MT, Barco R. Application of adipose tissue-derived stem cells in a rat rotator cuff repair model. Injury 2014;45(Suppl. 4):S22–7.
[86] Fukuchi Y, Nakajima H, Sugiyama D, Hirose I, Kitamura T, Tsuji K. Human placenta-derived cells have mesenchymal stem/progenitor cell potential. Stem Cells 2004;22(5):649–58.
[87] Ma R, Schaer M, Sisto ML, Chen KY, Wang H, E.Z G, et al. Use of placental-derived adherent stromal cells improves healing in a pre-clinical model of tendon injury. New Orleans, Louisiana: American Academy of Orthopaedic Surgeons (AAOS) 2014 annual meeting; 2014.
[88] Adams JE, Zobitz ME, Reach Jr JS, An KN, Steinmann SP. Rotator cuff repair using an acellular dermal matrix graft: an in vivo study in a canine model. Arthroscopy 2006;22(7):700–9.
[89] Dejardin LM, Arnoczky SP, Ewers BJ, Haut RC, Clarke RB. Tissue-engineered rotator cuff tendon using porcine small intestine submucosa. Histologic and mechanical evaluation in dogs. Am J Sports Med 2001;29(2):175–84.
[90] Nicholson GP, Breur GJ, Van Sickle D, Yao JQ, Kim J, Blanchard CR. Evaluation of a cross-linked acellular porcine dermal patch for rotator cuff repair augmentation in an ovine model. J Shoulder Elbow Surg 2007;16(Suppl. 5):S184–90.
[91] Iannotti JP, Codsi MJ, Kwon YW, Derwin K, Ciccone J, Brems JJ. Porcine small intestine submucosa augmentation of surgical repair of chronic two-tendon rotator cuff tears. A randomized, controlled trial. J Bone Joint Surg Am 2006;88(6):1238–44.
[92] Walton JR, Bowman NK, Khatib Y, Linklater J, Murrell GA. Restore orthobiologic implant: not recommended for augmentation of rotator cuff repairs. J Bone Joint Surg Am 2007;89(4):786–91.
[93] Badhe SP, Lawrence TM, Smith FD, Lunn PG. An assessment of porcine dermal xenograft as an augmentation graft in the treatment of extensive rotator cuff tears. J Shoulder Elbow Surg 2008;17(Suppl. 1):35S–9S.
[94] Soler JA, Gidwani S, Curtis MJ. Early complications from the use of porcine dermal collagen implants (Permacol) as bridging constructs in the repair of massive rotator cuff tears. A report of 4 cases. Acta Orthop Belg 2007;73(4):432–6.
[95] Sears BW, Choo A, Yu A, Greis A, Lazarus M. Clinical outcomes in patients undergoing revision rotator cuff repair with extracellular matrix augmentation. Orthopedics 2015;38(4):e292–6.
[96] Giannotti S, Ghilardi M, Dell'osso G, Magistrelli L, Bugelli G, Di Rollo F, et al. Study of the porcine dermal collagen repair patch in morpho-functional recovery of the rotator cuff after minimum follow-up of 2.5 years. Surg Technol Int 2014;24:348–52.
[97] Gilot GJ, Alvarez-Pinzon AM, Barcksdale L, Westerdahl D, Krill M, Peck E. Outcome of large to massive rotator cuff tears repaired with and without extracellular matrix augmentation: a prospective comparative study. Arthroscopy 2015;31(8):1459–65.
[98] Barber FA, Burns JP, Deutsch A, Labbe MR, Litchfield RB. A prospective, randomized evaluation of acellular human dermal matrix augmentation for arthroscopic rotator cuff repair. Arthroscopy 2012;28(1):8–15.
[99] Wong I, Burns J, Snyder S. Arthroscopic GraftJacket repair of rotator cuff tears. J Shoulder Elbow Surg 2010;19(Suppl. 2):104–9.
[100] Ciampi P, Scotti C, Nonis A, Vitali M, Di Serio C, Peretti GM, et al. The benefit of synthetic versus biological patch augmentation in the repair of posterosuperior massive rotator cuff tears: a 3-year follow-up study. Am J Sports Med 2014;42(5):1169–75.
[101] Proctor CS. Long-term successful arthroscopic repair of large and massive rotator cuff tears with a functional and degradable reinforcement device. J Shoulder Elbow Surg 2014;23(10):1508–13.
[102] Barbash S, Denny C, Collin P, Reish T, Hart JM, Brockmeier SF. Clinical outcomes and structural healing after arthroscopic rotator cuff repair reinforced with a novel absorbable biologic scaffold: a prospective multicenter trial. Orthop J Sports Med 2015;3(Suppl. 2).
[103] Vitali M, Cusumano A, Pedretti A, Naim Rodriguez N, Fraschini G. Employment of synthetic patch with augmentation of the long head of the biceps tendon in irreparable lesions of the rotator cuff: our technique applied to 60 patients. Tech Hand Up Extrem Surg 2015;19(1):32–9.
[104] Bernuzzi G, Petraglia F, Pedrini MF, De Filippo M, Pogliacomi F, Verdano MA, et al. Use of platelet-rich plasma in the care of sports injuries: our experience with ultrasound-guided injection. Blood Transfus 2014;12(Suppl. 1):s229–34.
[105] Bubnov R, Yevseenko V, Semeniv I. Ultrasound-guided injections of platelets rich plasma for muscle injury in professional athletes. Comparative study. Med Ultrasonography 2013;15(2):101–5.
[106] Wright-Carpenter T, Klein P, Schaferhoff P, Appell HJ, Mir LM, Wehling P. Treatment of muscle injuries by local administration of autologous conditioned serum: a pilot study on sportsmen with muscle strains. Int J Sports Med 2004;25(8):588–93.
[107] Gerber C, Meyer DC, Fluck M, Benn MC, von Rechenberg B, Wieser K. Anabolic steroids reduce muscle degeneration associated with rotator cuff tendon release in sheep. Am J Sports Med 2015;43(10):2393–400.
[108] Oh JH, Kim SH, Kim JH, Shin YH, Yoon JP, Oh CH. The level of vitamin D in the serum correlates with fatty degeneration of the muscles of the rotator cuff. J Bone Joint Surg Br 2009;91(12):1587–93.