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Biologics in rotator cuff surgery

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Abstract

Pathologies of the rotator cuff are by far the most common cause of shoulder dysfunction and pain. Even though reconstruction of the rotator cuff results in improved clinical outcome scores, including decreased pain, several studies report high failure rates. Orthopaedic research has therefore focused on biologically augmenting the rotator cuff reconstruction and improving tendon–bone healing of the rotator cuff. This biological augmentation has included the application of different platelet concentrates containing growth factors, mesenchymal stem cells, scaffolds and a combination of the above. The present review provides an overview over the biological augmentation options based upon current evidence.

Keywords

Biological augmentation, growth factors, rotator cuff healing, scaffold, shoulder surgery, stem cells, tendon-bone healing

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Introduction

Pathologies of the rotator cuff are by far the most common cause of shoulder dysfunction and pain. Rotator cuff tendon repair is a common procedure. Even though reconstruction of the rotator cuff results in improved clinical outcome scores, including decreased pain, several studies report failure of healing in up to 94% of patients.[1] The reason for these high failure rates can be found in intrinsic degenerative changes in the tendon, the rather low cellularity and the poor blood supply of the enthesis.

In the past two decades, orthopaedic research has focused on biologically augmenting the rotator cuff reconstruction and therefore improving tendon–bone healing of the rotator cuff. This biological augmentation has included applying different platelet concentrates containing growth factors, mesenchymal stem cells (MSCs), scaffolds and a combination of the above. The present review provides an overview over the biological augmentation options based upon current evidence.

Cytokine-based augmentation

Different growth factors have been reported to play an important role in the tendon–bone healing. Cytokines are proteins that act as signalling molecules regulating cell proliferation, cell migration, cell differentiation, matrix synthesis and inflammation.

The use of individual cytokines for augmentation of the rotator cuff has been investigated in different animal models but, to our knowledge, not in a clinical study.

The healing process is regulated not only by one single cytokine, but also by an abundance of different signaling proteins. It therefore makes sense to also apply a mixture of cytokines to the healing site instead of only one specific growth factor. In a sheep rotator cuff model, Rodeo et al. implanted bone morphogenetic protein (BMP)-2 to BMP-7, transforming growth factor (TGF)-β1 to TGF-β3, and fibroblast growth factor in a collagen type I sponge between the tendon and the footprint.[2] After 6 weeks and 12 weeks, an increased maximal load to failure, as well as an increased bone- and soft tissue volume, was found compared to the control group, where a reconstruction but no biological augmentation was performed. However, when normalized to the tissue volume, no differences were found. These data suggest that a mixture of the

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implanted cytokines accelerates the healing process but does not change the quality of the repair. Similar results were found when single growth factors (e.g. BMP-12[3] or TGFβ[4]) were used in animal models to augment rotator cuff healing.

To date, no clinical data exists with respect to the application of a single or multiple cytokines to the rotator cuff reconstruction.

Application of platelet-rich concentrates in rotator cuff repair

During tendon–bone healing, several different growth factors are involved in the healing process. Platelet concentrates contain more than 1500 bioactive substances, including many growth factors that are important for the healing, namely TGF-β1, platelet-derived growth factor, basic fibroblast growth factor, vascular endothelial growth factor, endothelial growth factor and insulin-like growth factor-1. Autologous platelet concentrates are available without the risk associated with allogenic products and they can be produced in less than 30 minutes during rotator cuff reconstruction.

Platelet concentrates have therefore been explored as a potential and promising biological augmentation for healing. Preclinical *in vitro* studies have shown promising results, although only a couple of large scale clinical studies have investigated its benefit for the healing rotator cuff with inconclusive results. A limiting factor is that several different platelet concentrates exist, each one showing different properties in the growth factor release over time. The reasons for these different properties may be found in the lack of standardization between the different platelet concentration systems, with every system showing different concentration factors and activation status of the platelets. Other reasons for the differences between these systems may also be found in the differing concentrations of other bioactive ingredients, such as leukocytes, red blood cells and the fibrinogen.

For this reason, we have categorized the different larger-scale clinical studies presented in the present review depending on their leukocyte and fibrin content into four different categories as proposed by Dohan Ehrenfest et al.[5]:

1. L-PRF (leucocyte and platelet rich fibrin), such as L-PRF
2. P-PRF (pure platelet-rich fibrin), such as the Cascade Medical *FIBRINET* PRFM System (Cascade Medical, Wayne, NJ, USA)
3. L-PRP (leucocyte- and platelet-rich plasma), such as GPS III (Biomet Inc, Warsaw, Indiana, USA), Magellan (Arteriocyte Medical Systems, Cleveland, OH, USA) and SmartPReP Harvest Technologies Corp., Plymouth, MA, USA
4. P-PRP (pure platelet-rich plasma), such as Vivostat A/S, Denmark

Leukocyte and platelet-rich fibrin (L-PRF). In a randomized controlled trial study,[26] Zumstein et al. investigated the clinical and radiographical benefit of augmenting rotator cuff repairs using L-PRF. The patients ($n = 10$), in whom L-PRF was added during the rotator cuff repair, showed an increased vascularization 6 weeks ($p = 0.001$) after surgery compared to a control group of patients ($n = 10$), who did not receive L-PRF. Clinical examinations, including subjective shoulder value and the visual analogue scale, as well as Constant and the Simple Shoulder Test scores, did not reveal significant differences after 6 weeks and 12 weeks. A limitation of the study is the rather small sample size.[26]

Pure platelet-rich fibrin (P-PRF). In a randomized controlled trial, Rodeo et al. performed a rotator cuff reconstruction in 79 patients.[7] 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 and the clinical outcome between the two groups. Of interest, 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) because it was a significant predictor for a tendon defect at 12 weeks. Castricini et al. reported similar results.[8] No significant difference was found when comparing the Constant Score ($p = 0.44$) and the re-rupture 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 groups. Also, no difference was found between both groups when comparing the tendon thickness ($p = 0.18$). However, the results are only applicable for small and medium rotator cuff tears.

Leukocyte and platelet-rich plasma (L-PRP). In a controlled prospective randomized study, Randelli et al. performed a rotator cuff reconstruction in 53 subjects.[9] In the treatment group ($n = 26$), the rotator cuff reconstruction was biologically augmented by applying L-PRP. In the control group ($n = 27$), the rotator cuff was reconstructed without L-PRP treatment. The patients in the treatment group showed reduced pain in the first 30 postoperative days and an increased Simple Shoulder Test after 3 months. There were no clinical and radiographical differences between the two groups after 6 months, 12 months and 24 months.

Gumina et al. reported that augmentation of a rotator cuff reconstruction using a platelet-leukocyte membrane that contains platelets only 1.7 times greater than in normal blood improved repair integrity compared to a control group ($p = 0.04$), where a conventional reconstruction was performed.[10] They did not find any difference in clinical outcome.

Pure platelet-rich plasma (P-PRP). In a recently published randomized, single-blinded study, 48 patients were randomly assigned to receive either a P-PRP augmented (24 patients) or a conventional (24 patients) rotator cuff reconstruction after a large or massive rotator cuff tear. A leucoreduction plasmapheresis system was used for the production of P-PRP. Patients in the P-PRP group showed a significant lower retear rate (20.0% versus 55.6%) and a less pronounced change of the cross sectional area from immediately postoperative to the 1-year follow-up [PRP group: –15.54 (94.34) mm^2; control group: –85.62 (103.57) mm^2]. A limitation of the study is the rather small sample size.[11]

Another pilot study, where the Vivostat system was used, showed no differences in the clinical outcome, nor in the re-tear rate up to 24 postoperatively.[12] A limitation of this study is the rather small sample size.

Cell-based augmentation

Tendons contain relatively few cells. Low cellularity coupled with hypovascularity results in a poor healing response, especially in an overuse model in the rotator cuff. In response to this problem, the influence of the biological augmentation using cells has been investigated.

Application of stem cells

Biological augmentation of the enthesis using stem cells has been a considerable research focus over recent years. Stem cells can be classified according to their ability to differentiate into other cell types. Therefore, they can be divided into the following categories:

Embryonic stem cells

Totipotent stem cells. These cells can divide into every cell of an organism. Embryonic cells within the first couple of cell divsions are the only cells that are totipotent.

Pluripotent stem cells. These cells can still divide into every cell type in an organism, except for the extra embryonic tissue (i.e. they can not divide into a cell that becomes the placenta).

Multipotent stem cells. These cells can divide into a limited range of cells of a single tissue type. Multipotent blood stem cells, for example, can divide into red or white blood cells or platelets but not into muscle cells.

Adult stem cells. Adult stem cells are multipotent undifferentiated cells found in adult tissue. They can replace different dying cells in a tissue. MSCs and adipose-derived stem cells (AD-MSCs) belong to this category. These cells are adult stem cells but, unlike MSCs and AD-MSCs, which are multipotent, the placenta-derived stem cells are pluripotent. They have the capacity to differentiate toward all three germ layers.[13]

Embryonic stem cells offer a wider therapeutic potential than adult stem cells, especially when using totipotent cells. However, their use in research is ethically controversial and there is an increased risk for teratoma development when using embryonic stem cells. Adult stem cells avoid the ethical issues and malignant transformationis much less likely. These cells additionally offer the possibility of autologous stem cell transplantation; for example, using bone marrow-derived MSCs.

Application of MSCs in rotator cuff repair. Evidence suggests that mesenchymal stromal cells (MSCs) might provide additional impetus for restoration of the tendon–bone interface, ultimately reducing failure rates and improving shoulder function. Therefore, applying bone marrow aspirate concentrate, which contains MSCs, represents a promising option for a biological augmentation of the rotator cuff repair healing. However, a safe, effective and appropriate delivery of these bioactive agents is yet to be optimized.

To date, there is limited evidence regarding whether the biological augmentation using MSCs improves the healing of the rotator cuff in human. In a recently published study, 14 patients with complete rotator cuff tears received a rotator cuff reconstruction with a subsequent injection of autologous bone marrow-derived stem cells.[14] Magnetic resonance imaging analysis, which was performed 12 months after surgery, revealed a 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, which was considered to be a bad result.[14] However, a limitation of the 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. were able to harvest MSCs from the bone marrow through the anchor tunnel of the humeral head during arthroscopic rotator cuff repair.[15] These cells then were cultivated. In this way, it was possible to produce connective tissue progenitor cells that 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.[16] It was possible to show that these cells differentiated into cells with characteristics consistent with tendon.[16] The potential for MSCs to differentiate into tendon after a single dose of insulin may assist in developing practical biological options for augmentation of rotator cuff repairs. 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.[17] The subacromial tissue showed more passage 0 cells and these cells maintained their proliferative ability for more passages. They also showed a higher osteogenic and adipogenic potential. Only the chondrogenic potential in subacromial MSCs was lower compared to the MSCs harvested from the enthesis. An interpretation of these *in vitro* results is difficult and the proposed conclusion that subacromial bursa MSCs are a good candidate for the source of MSCs in rotator cuff tears is questionable. Not a high adipogenic but a chondrogenic potential would be desirable for healing of the enthesis because two out of the four physiological zones in the rotator cuff enthesis consist of fibrocartilage. However, exactly this chondrogenic potential is rather low in the subacromial bursa MSCs.

Application of adipose-derived stem cells in rotator cuff repair. Another source of MSCs is fatty tissue. Adipose-derived stem cells (AD-MSCs) can be harvested via the relatively minimal invasive liposuction. 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.[18]

When injected into a chronic rotator cuff healing model in the rabbit, AD-MSCs increased the maximal load to failure compared to the group where only saline was injected into the repair site.[19] However, this difference was not statistically significant. Furthermore, subscapularis muscle in which AD-MSCs were injected showed less fatty infiltration with a fat content of only 29% (15%) compared to 43% (9%) in the control group.[19]

AD-MSCs might represent a good alternative to increase tendon–bone healing in the rotator cuff and to improve the structure of the rotator cuff muscle. Clinical studies will be necessary to demonstrate any benefit in humans.

Application of placental-derived stem cells in rotator cuff repair. Placental human-derived MSCs were shown to have multilineage differentiation potential similar to MSCs derived from bone marrow.[20] These cells can be isolated and expanded easily, thus making these cells attractive for the biological augmentation of the rotator cuff. Further *in vitro* and clinical studies are necessary to explore their safety and potential in orthopaedics.

Scaffold-based augmentation

Scaffolds have been investigated for decades for surgical use. These scaffolds can be divided into allografts, xenografts and synthetic scaffolds. These grafts may increase the initial strength of the reconstruction, protect the repair and then provide gradual stress transfer to the healing tissue, and allow tissue ingrowth. Only a limited number of clinical studies have been conducted in which the clinical and radiographical outcome after augmentation of rotator cuff repairs using scaffolds has been investigated. In the present review we will focus on xenografts and allografts only.

Xenografts

Even though augmentation using porcine small intestine submucosa was shown to improve healing in the animal Achilles tendon, clinical studies, where large to massive chronic rotator cuff tears were augmented using a similar scaffold (Restore Orthobiologic Implant; DuPuy Orthopaedics, Warsaw, IN, USA), showed no differences in clinical outcome compared to a control group.[21]

Another group reported that four out of 19 (21%) patients treated with the same xenograft had had a severe postoperative inflammatory reaction, which made reoperation with a debridement and removal of the graft necessary. Because all the intraoperative cultures were negative, this reaction was most likely caused by the xenograft. Furthermore, no clinical benefit could be shown after a 2-year follow-up.[22]

Inconsistent results were reported when using Permacol (Zimmer Collagen Repair Patch; Zimmer Inc., Warsaw, IN, USA). Permacol is an acellular porcine dermal collagen matrix. It is cross-linked and thus not susceptible to enzymatic degradation. Badhe et al. reported good results 4.5 years after augmenting massive rotator cuff tears in 10 patients, with an intact repair in eight patients and a retear in only two patients.[23] Soler et al. on the other hand were using Permacol as a bridging device.[24] All four reconstructions failed within 6 months postoperatively and had signs of inflammation.

Allograft

Better results were found when using GraftJacket (Wright Medical Technology, Inc., Memphis, TN,

USA) allograft acellular human dermal matrix for augmentation of large to massive rotator cuff tears[25,26] In a prospective, randomized study, an arthroscopic rotator cuff reconstruction of rotator cuff tears larger than 3 cm was performed with either a GraftJacket augmentation ($n = 20$) or without augmentation ($n = 22$).[25] After a follow-up of 12 months 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.

Conclusions

There is a great need for biological augmentation of rotator cuff tears as a result of the high retear rate after rotator cuff reconstruction. There is a significant lack of knowledge with respect to the complicated interaction of cytokines, cells and the extracellular matrix during the healing of the rotator cuff enthesis. Cytokines have shown the potential to improve the rotator cuff healing in animal models, although little information exists about the correct concentration and timing of the more than 1500 cytokines that interact with the healing site during the healing process. To identify the right combination, timing and concentration of cytokines, further studies are required. Using cells to biologically augment represents another important evolving field. In particular, stem cells might have great potential because 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 for augmentation of rotator cuff tears.

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