# 5 Biological Augmentation in Rotator Cuff Repair: Growth Factors

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Currently, roughly 250,000 rotator cuff repairs per year are performed in the United States alone [1]. Retear rates especially in massive rotator cuff tears are still an issue. We are still facing up to 94% retear rate in large to massive rotator cuff tears even with double-row repairs [2, 3] while the clinical importance of retears remains unclear [4–6].

Retears of tendons have been associated with the same patho-mechanisms that led to the initial tear: mechanical stress on a degenerated tendon. This might lead to retearing just medial to the repair site [7, 8].

In a prospective trial, tendon pulling through the sutures is the most common type of failure (so-called cheese wiring) followed by new tears through the already degenerated tissue and anchor failure, respectively [8]. It was also found that retears are a multifactorial process associated with tear size [9].

One possible solution to this problem might be to augment rotator cuff repairs with matrices, patches, or growth factors. Reinforcing the rotator cuff with synthetic or xenografts adds a high complexity to arthroscopic rotator cuff repair while mixed results have been reported [10, 11].

Due to promising animal studies, the use of growth factors such as platelet-rich plasma (PRP) has been implemented as an alternative. It was hypothesized that PRP would improve rotator cuff healing by propelling regeneration of the degenerated tendons by means of stimulating the differentiation of scar tissue [7, 12]. Platelet-rich plasma (PRP) is the most commonly used term for an autologous, concentrated platelet suspension. Autologous conditioned plasma (ACP) is another platelet suspension form with a low level of white blood cells. Autologous conditioned serum (ACS) is a platelet suspension which has a high content of IL-1Ra (Interleukin-1 receptor antagonist) and is therefore used for anti-rheumatic and anti-inflammatory purposes. Direct comparisons of individual products have shown a relatively large variability of the contents, and for use in clinical practice a great overlap of PRP/ACP/ACS in nature and effect can be assumed [13].

In clinical practice, PRP was initially used primarily in plastic, cardiovascular, and maxillofacial surgery [14, 15]. Early studies in these fields have shown beneficial effects on wound healing, tissue regeneration, and fracture healing/bone remodeling. Responsible for this were bioactive proteins and growth factors [16, 17]. However, the extracellular matrix of the coagulated PRP has also been discussed as a potential

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signaling mechanism for regenerative processes because of its mechanical and structural properties [18]. Furthermore, it was confirmed that the autologous cells do not induce any unwanted immunological reactions or even diseases that may be associated with blood transfusions, for example. In short, PRP therapy can fill or cover a defect, locally release growth factors that attract the cells needed for wound healing, and stimulate these cells to increased activity. In the context of these processes, a PRP therapy can stimulate and sustain wound healing.

PRP preparations at various cell concentrations are used both experimentally and clinically. Unequivocal evidence for optimal platelet concentration does not exist so far, and the relationship between concentration and effect is unclear. Some arguments suggest that high concentration produces a high impact, and most commercial kits produce PRP in the range of 9–14× physiological platelet concentration. Others, in turn, could not show any clinical differences with higher concentrations, or even report detrimental effects, e.g., the inhibition of osteoblasts [19]. For example, animal experiments have shown equally good biomechanical results for ligament and tendon regeneration with 3–5× concentrated PRP compared to higher concentrations [20]. This could also be shown specifically for human rotator cuff cells [21]. Finally, it could even be shown that a 1.2–2× concentration of PRP, i.e., nearly normal blood, can achieve a good effect in soft tissue healing [20]. Too high a concentration of growth factors may result in an unorganized reaction of the cells involved in healing, resulting in a poorly differentiated, i.e., mechanically weak, scar [22]. PRP is not a pure platelet suspension, and with ACP or ACS even a reduced addition of white blood cells is advertised. Both red blood cells and leukocytes have been shown to modulate the effect of platelets on mesenchymal cells [23]. Due to the fact that PRP is supposed to support but not overstimulate wound healing, this interaction with erythrocytes and leukocytes is desirable, although the evidence here is less. Currently, there is no gold standard regarding the ion or electrolyte concentration, nor is it determined how high the protein fraction should be.

Lastly, the application form of PRP is a matter of debate. It can be injected as a suspension, or used as a spray or as a gel (on a carrier). There is very little comparative data on these applications or on the effect depending on the application form. However, influence on the enzyme kinetics by the application form is probably nonexistent. What needs to be considered, especially in the context of an arthroscopic application, is feasibility. A solid clot can be manipulated and threaded on a suture. A fluid application is at risk of dilution or to be flushed out of the defect.

Promising results are obtained from animal studies. Recently, it was shown that a freeze-dried chitosan implant solubilized in PRP could enhance tendon-to-bone healing and thus improve rotator cuff healing in a rabbit model [24].

In our systematic review, we could show that the use of PRP did not improve tendon healing and reduce retears in large tears but was beneficial in small- and medium-sized tears [25].

Alternatively, microfracturing of the humeral head in order to influx connective tissue progenitor cells into the healing site during rotator cuff repair has been advocated [26]. A recent meta-analysis revealed a positive effect to reduce retear rates by promoting tendon-to-bone healing [27]. However, no significant improvement in clinical outcomes was shown.

**Cost-Effectiveness**

In recent years, terms like cost-effectiveness, value-based health care, and sustainability in health care financing have become ubiquitous and physicians are increasingly confronted with demands for cost-effectiveness and cost-containment by legislators and insurance companies. Hence it makes sense to approach biological augmentation not only from a clinical-impact perspective, but also from one of economic feasibility. A simple economic analysis has two scopes. In the narrow scope, the question whether the incremental cost of adding growth factors to a cuff repair is offset by a commensurate gain in clinical outcome needs to be answered. In the wider scope, the question whether the incremental cost of adding growth factors to a cuff repair that is offset by a commensurate gain in clinical

outcome is preferable to a surrogate treatment form (e.g., an RSA).

For the smaller scope, some data exist to build an analytical model. This model includes the various possible developments of a patient undergoing cuff repair (i.e., healing, retear, and revision) into a decision tree. Each branch represents a specific outcome with the likelihood of achieving this outcome. A value, called *utility*, for each outcome is developed from patient information. The utility describes the value of an event or outcome to a patient and its unit of measurement is the quality-adjusted life year (QaLY). The utility of healing obviously is higher than the utility of a retear. The utility of a successful revision is lower than the utility of a successful primary repair due to a principle called *time preference*. Time preference describes the simple fact that achieving a preferred outcome sooner has a higher utility than arriving at the same endpoint later or via a circuitous route. For economic analysis, the gain of utilities is compared to the additional cost, usually within a range of outcomes (i.e., with a risk of revision ranging from +10% to −10% of what is seen in the literature) to account for clinical variability. The findings are compared to benchmarked thresholds, with a rule of thumb that an extra cost of US$ 100,000.00 for an additional QaLY is considered cost-effective. One study exists using such a standardized framework to assess the cost-effectiveness of biological augmentation of cuff repair with PRP. Its findings show that the overall cost (including consumables, OR time, and fixed cost) should be below (2015) US$ 650. Given the current cost of most commercially available kits, and the mostly negative growth of reimbursement rates of shoulder surgery it is questionable if this is a sustainable business case outside well-structured ASCs and comparable institutions. However, microfracturing as described above has very little additional cost in time and consumables.

In the larger scope, confronted with a massive or irreparable cuff tear, substitutes to arthroscopic repair exist and are well delineated and described in following chapters. A considerably larger decision model could include cuff repair, shoulder replacement, debridement, spacers, etc. like the model described above. There is some data on the comparison of cuff repair with primary replacement in patients with massive tears favoring cuff repair in the short- and mid-term. However, this hinges to a greater extent on the lower initial cost of arthroscopic repair, a low revision rate, and no arthritic degeneration, rather than on clinical outcomes. This preference changes drastically if a cuff repair is to be revised. Hence, the additional cost of PRP in cuff repair, if reducing revision-worthy retears, may be well within cost-effectiveness thresholds. We could show that although retear rates can be reduced in small- and mid-size tears using PRP this procedure is not cost-effective [25].

In conclusion, the use of growth factors, especially PRP, does not reduce retear rates and is currently not cost effective due to the additional OR time and costs of the harvesting systems. However, results from animal studies using structural grafts loaded with PRP are promising. Upon reviewing the current literature, the authors have the impression that we are at a turnaround to enhance tendon healing with growth factors using scaffolds [28, 29]. Currently, the easiest and most cost-effective procedure is microfracturing of the tuberosities to get stem cells into the healing site [27].

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