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REVIEW ARTICLE

Effectiveness of Biologic Factors in Shoulder Disorders

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Abstract:

Background:

Shoulder pathology can cause significant pain, discomfort, and loss of function that all interfere with activities of daily living and may lead to poor quality of life. Primary osteoarthritis and rotator cuff diseases with its sequalae are the main culprits. Management of shoulder disorders using biological factors gained an increasing interest over the last years. This interest reveals the need of effective treatments for shoulder degenerative disorders, and highlights the importance of a comprehensive and detailed understanding of the rapidly increasing knowledge in the field.

Methods:

This study will describe most of the available biology-based strategies that have been recently developed, focusing on their effectiveness in animal and clinical studies.

Results:

Data from *in vitro* work will also be briefly presented; in order to further elucidate newly acquired knowledge regarding mechanisms of tissue degeneration and repair that would probably drive translational work in the next decade. The role of platelet rich-plasma, growth factors, stem cells and other alternative treatments will be described in an evidence-based approach, in an attempt to provide guidelines for their clinical application. Finally, certain challenges that biologic treatments face today will be described as an initiative for future strategies.

Conclusion:

The application of different growth factors and mesenchymal stem cells appears as promising approaches for enhancing biologic repair. However, data from clinical studies are still limited, and future studies need to improve understanding of the repair process in cellular and molecular level and evaluate the effectiveness of biologic factors in the management of shoulder disorders.

Keywords: Biologic factors, Effectiveness, Growth factors, Healing, Osteoarthritis, Platelet rich-plasma, Rotator cuff, Stem cells.

INTRODUCTION

Shoulder joint disorders cause chronic pain and functional disability influencing adversely the quality of life. Particularly, shoulder pain is considered as one of the three most common causes of musculoskeletal complaints [1]. Most commonly reported shoulder disorders include traumatic and degenerate tears of the rotator cuff (RC) (RC tendinopathy), subacromial impingement syndrome and bursitis, frozen shoulder, bicipital tendonitis, and glenohumeral/acromioclavicular arthritis [2].

Among them, two major disorders are identified; RC tendinopathy and osteoarthritis (OA). RC tendon pathology is

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reported as the source of approximately 30-70% of shoulder pain disorders [1, 3, 4]. Interestingly, more than 50% of the patients older than 60 years-old demonstrate pathologies, such as RC impingement and partial- or full-thickness tear [5]. Shoulder OA is another common disorder that causes disability and pain, with an increasing incidence after the age of 50 years old [6, 7]. Over the last years, an increasing incidence of shoulder disorders is reported, indicating more comprehensive diagnosis and improved understanding in the related pathology and treatment [6 - 8]. The significance of shoulder disorders becomes clear when considering the emerge of new treatment approaches and the increased burden of shoulder pain that results in higher cost of treatment over the last decades [3, 4, 9 - 11].

The etiopathogenesis of shoulder disorders is far more complex than in load bearing joints, due to the fact that shoulder joint withstands a wide range of compressive, shear, and tensile loads [12, 13]. RC pathology has been attributed to intrinsic or extrinsic theories. The first involves the theories of hypoperfusion, degeneration, microtrauma and apoptosis, while the second refers to chronic impingement syndrome, overuse and other multifactorial causes of progressive degeneration [14 - 20]. Regardless the etiologies, shoulder diseases concerning especially the RC, alter progressively the shape of acromion, causing further narrowing of the subacromial space. Furthermore, upward migration of the humeral head after rotator cuff deficiency also contributes in inflammation, pain, and potential functional limitation [1, 4, 21, 22]. Similarly, for glenohumeral cartilaginous degeneration, several factors have been considered risk factors, such as trauma, (impact and joint dislocation), osteonecrosis, inflammatory disorders, and infection [23 - 26].

Management of shoulder disorders includes conservative treatment, which involves analgesics, anti-inflammatory drugs, local anesthetics, steroid injections and physiotherapy, and, when conservative treatment fails, open or arthroscopic surgery for more advanced disorders. Debridement of the degenerative tissue or repair of the rotator cuff tear with re-attachment of the ruptured tendon to the bone with non-absorbable sutures, may offer significant pain relief. When osteoarthritis develops, the only viable treatment option is joint reconstruction. However, both conservative and operative treatment may have limitations, be ineffective or lead to repair failure. For instance, in cases of large massive tears with extreme degeneration and poor tissue quality, the rate of healing failure is considerably high, estimated at up to 75% [27 - 32]. Therefore, further improvement of treatment success in shoulder disorders is a critical aspect of patient care.

Several risk factors for tendon repair failure have been identified, both patient-related and management related. For example, patient`s age and smoking are among the most important factors for re-tear [33 - 36]. Further, insufficient suture strength, size, and chronicity of tear are also implicated in tissue healing [32, 36 - 38]. Tendon advanced degeneration, as it occurs in late tears, is characterized by reduced cell numbers, poor matrix organization, and poor vascularization, thus, preventing full capacity of tissue healing [39 - 42]. On the other hand, the occurrence of failures in shoulder disorders repair even in younger age might imply the presence of conditions in the healing process associated with biologic factors that are expressed early in the repair phase (Fig. **1**) [39, 43]. Since large chronic RC tears have high failure rates certain factors exist in those cases that are implicated in the failure of rotator cuff repairs [27]. It has become apparent that the rate-limiting step is the inability of the healed tendon to mimic the structural and functional characteristics of native enthesis, the normal tendon-to-bone transition zone [44, 45]. Instead of a four-zone structure rich in type I collagen, the healed tendon-to-bone interface is characterized by a layer of fibrocartilage rich in collagen type III [44, 45]. It is the quality of tendon-bone healing that appears to be most probably responsible for the high failure rate of rotator cuff repair.

Several new techniques present promising data that could potentially change the treatment approach to shoulder pathology as known today [10, 23]. In that aspect, great concern has been expressed towards improving the biological environment and tissue's healing capacity [46 - 52]. The usage of biologic factors can be proven as an essential key for more effective management of shoulder disorders at an earlier stage [46 - 52]. Biologics can be used either as part of conservative management or as adjuvants to surgical therapy.

The interest in biologic repair in shoulder has increased enormously over the last 5 years. As shown in Fig. (**2**), the number of studies published about "biologic factors" and "rotator cuff" (used as the most representative and popular condition for shoulder specific pathology) has rapidly increased over the last 5 years (Fig. **2a**). Similar exponential trend in the published studies was also observed when the search in PubMed, Web of Science, and Scopus databases included the terms "stem cells" and "rotator cuff" (Fig. **2b**). This interest is indicative for the need of alternative effective treatments for shoulder disorders, and highlights the need of a comprehensive and detailed knowledge of the rapidly increasing amount of the relevant literature.

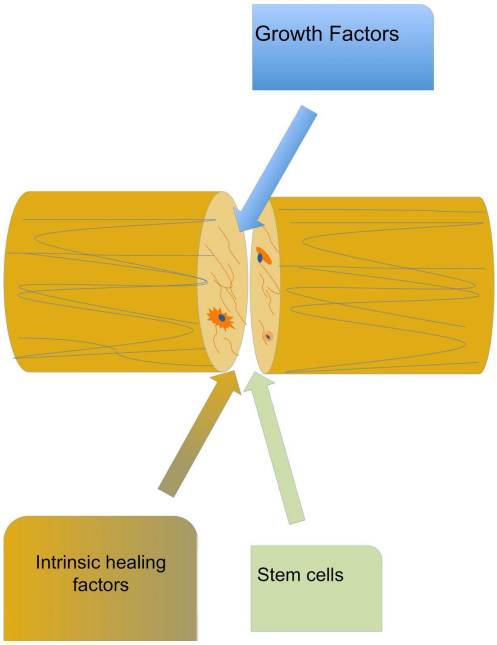

Fig. (1). Main biologic factors that are associated with tendon healing process.

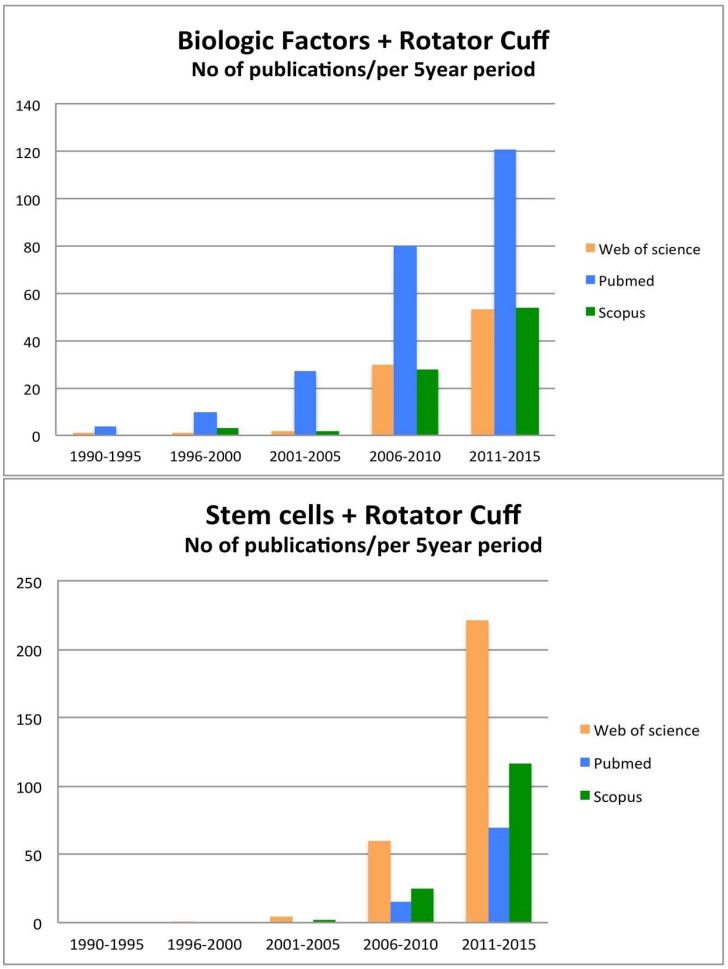

Fig. (2). (a). Number of studies published regarding biological factors and rotator cuff per 5-year period in Web of Science, PubMed, and Scopus databases. **(b).** Number of studies published regarding stem cells and rotator cuff per 5-year period in Web of Science, PubMed, and Scopus databases.

The purpose of the review is to summarize the numerous biology-based strategies that have been proposed for both non-operative and surgical management of shoulder joint disorders *in vitro*, but most importantly in animal and clinical studies. We will focus on the effect of biological factors used in shoulder disorders, describing the role of platelet-rich plasma (PRP), and growth factor use. Furthermore, the findings of application of mesenchymal stem cells (MSC), matrix metalloproteinases (MMP) inhibitors, scaffolds, and gene therapy will be described. The emphasis will be on rotator cuff pathology, since the applications of biologic therapies for early shoulder osteoarthritis is limited, and mostly concern other joints, such as the knee.

PLATELET RICH PLASMA (PRP)

Platelet-rich plasma (PRP) gained popularity for shoulder disorders after introduced in the last decade as a biological component that could potentially improve rotator cuff tendinopathy [53, 54]. PRP is a fraction of whole blood with supra-physiological concentration of platelets, that, once activated, releases various growth factors, inflammatory cells, and proteins, that subsequently enhance stromal and mesenchymal stem cell proliferation and prevent fibrous scar tissue healing [41, 55, 56]. The preparation process includes separation of platelets from whole blood mainly through centrifugation, and a mixing step where agents that activate platelets are added [57 - 59]. The initial release of growth factors from alpha granules activates additional differentiation and secretion of growth factors after 7-10 days, which coincides with the inflammatory and repair phases of tendon [57, 60].

There is a wide variability among the different techniques for PRP preparation, which reflects the wide variability of the effectiveness of the prepared PRPs among the different studies [61]. The main growth factors that are released from platelets are transforming growth factor-beta (TGFb), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), hepatocyte growth factor, epithelial growth factor, and insulin-like growth factor 1 (IGF-1) [57]. These autologous growth factors are regarded as beneficial and accelerative for healing through cell proliferation, collagen regeneration, and revascularization [62 - 64]. Interestingly, the existence or not of these factors varies depending on the applied commercial system (*e.g.* number of available platelets, presence of anticoagulants and activators) with those containing higher leukocyte levels to be considered as more effective [65].

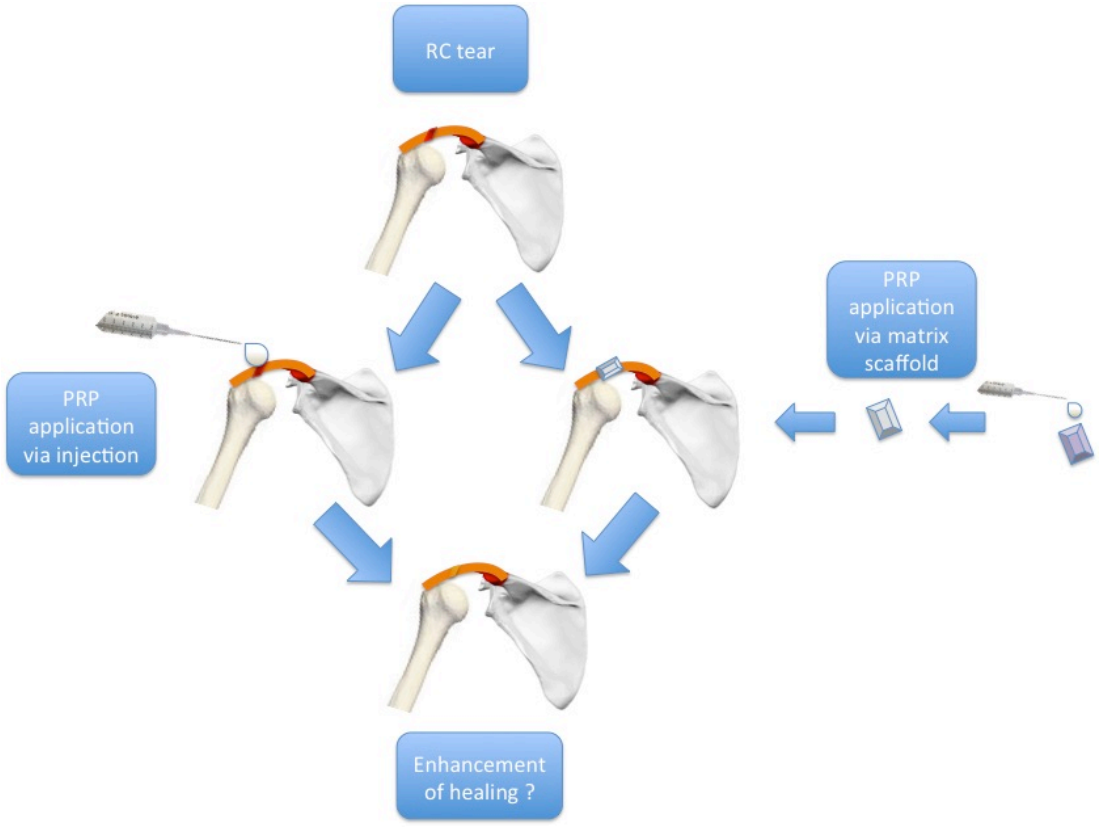

Fig. (3). Treatment strategies for biologic factor clinical application. An example of PRP use.

PRP can be applied over the repaired tissue, either directly with injection or through matrix scaffold [57] (Fig. **3**). In 2009, four categories of PRPs were defined based on the presence of leukocytes and fibrin architecture: a) Pure Platelet-Rich Plasma (P-PRP) – or Leukocyte-Poor Platelet-Rich Plasma (without leukocytes and with a low density fibrin network after activation). b) Leukocyte-and Platelet-Rich Plasma (L-PRP) (with leukocytes and a low-density fibrin network after activation). c) Pure Platelet-Rich Fibrin (P-PRF) – or Leukocyte-Poor Platelet-Rich Fibrin (without leukocytes and with a high-density fibrin network). d) Leukocyte-and Platelet-Rich Fibrin (L-PRF) (with leukocytes and a high-density fibrin network) [66, 67].

Matras in 1970 was the first who investigated the effect of growth factors released from PRP in skin wound healing of rats [68]. However, it was only the last decade that further investigation on the effects of different forms of PRP (*in vitro* or *in vivo*) on shoulder disorders was implemented. PRP injections for rotator cuff tendinopathy were shown to have promoting effects on tendon proliferation, collagen gene expression, and angiogenesis [41, 69]. Recently, these properties of PRP were confirmed *in vitro* demonstrating that growth factors released from PRP may improve cell proliferation of human tenocytes from degenerative rotator cuff and promote synthesis of extracellular matrix [70, 71].

Several *in vivo* animal studies were recently performed examining the effect of PRP on shoulder diseases. Enhancement of tendon-bone healing after local administration of autologous PRP in rabbits with chronic rotator cuff tears was evident, as assessed by histological and biomechanical testing [72]. Similar histological and biomechanical data with improved tendon-bone healing were reported after the application of intra-articular autologous PRP in rats during surgical repair after acute rotator cuff tear [73]. Another animal study showed enhancement of tendon-to-bone interface healing with PRP application regardless of the mode of application, *i.e.* injection *versus* sponge carrier [74].

Despite the theoretic basis and the promising results from *in vitro* and *in vivo* studies, there is a great controversy in the clinical practice for the effectiveness of different types of PRP on shoulder cuff disorders. In a meta-analysis, it was demonstrated that there was no clear clinical benefit or effect on the overall re-tear rate from the use of PRP after arthroscopic rotator cuff repair, especially for massive tears [75]. For medium to small tears it seems that there is a tendency of lower re-tear rate [75]. In particular, a prospective randomized double blind controlled level one study, included 88 patients with small to medium sized cuff lesions where the tears were repaired with a double row procedure [76]. No statistically significant differences were observed with the use of PRP at 16 months postoperatively, concerning both clinical and imaging parameters [76]. Another prospective randomized double-blind clinical trial demonstrated that there are only short-term (at 3 months) benefits regarding the clinical outcome (constant score, simple shoulder test and subjective shoulder value) and MRI, from the use of L-PRP injection during arthroscopic rotator cuff repair [77]. However, after 2 years follow-up, no statistical differences were stated concerning these parameters and only pain was lower in the L-PRP as compared to the control group [77]. In a prospective cohort study, it was observed that despite the fact that PRP gel application to arthroscopic rotator cuff repairs did not accelerate recovery in terms of pain, range of motion, strength, functional scores, or overall satisfaction, magnetic resonance imaging demonstrated a lower re-tear rate in the PRP group in comparison to the control group, but again, this did not reach a statistically significant difference [78]. Similar results were also demonstrated for PRP on at risk for failure rotator cuff repair, where the use of PRP increased the re-tear rate [79]. However, it cannot be ignored that in 2 out of 16 cases, there was a local infection [79].

More recently, a randomized controlled trial involving 60 patients, investigated the effect of postoperative, repeated, ultrasound-guided injections of PRP to the repaired supraspinatus tendon after double-row arthroscopic repair [80]. They found that there was no enhancement in early tendon-bone healing, functional recovery, range of motion, strength or pain [80]. A level one prospective randomized double-blind study that examined two groups of 27 patients each operated for cuff tear repair (PRP group *versus* control group) confirmed the above results [81]. PRP did not promote better clinical results at 24-month follow-up and there were no differences regarding the re-tear rate between the two examined groups [81]. The ineffectiveness of PRP to provide satisfactory results in arthroscopic cuff repair was also supported by another level one randomized, double-blind, controlled clinical trial of that found that the use of PRP in arthroscopic repair of rotator cuff tears was not beneficial for cuff healing with no functional (clinical assessments) or structural (arthro - magnetic imaging resonance (MRI)) improvements observed one year postoperatively [82]. In fact, in a prospective randomized level two study, platelet-rich plasma fibrin matrix (PRPFM) not only failed to show a positive effect on clinical outcome, but also may have a negative effect by altering the biological interface between tendon and bone [83].

On the other hand, a level three study that investigated the influence of PRPFM augmentation in two groups of 20 patients operated of a cuff repair with and without PRPFM, found a higher re-tear rate in the control group (without

PRPFM) as assessed by MRI [84]. In addition, a level one prospective randomized study which included patients operated with an arthroscopic single-row technique for large rotator cuff tear, reported better repair integrity in the PRP group (with platelet-leukocyte membrane) as compared to the control one (without platelet-leukocyte membrane) [85]. Application of PRP improved significantly structural outcomes for large to massive rotator cuff tears, as evidenced by a decreased re-tear rate, and improved shoulder function after 1-year follow-up [86]. It was also demonstrated that the use of autologous L-PRP was related with a lower re-tear rate in patients undergoing arthroscopic repair of large or massive rotator cuff tears, based on postoperative MRI evaluation [87]. However there was no correlation with the functional outcome 2 years postoperatively [87].

Regarding the role of PRP without a concurrent operative treatment of chronic rotator cuff tendinopathy, it was found that PRP injections were no more effective in improving quality of life, pain, disability, and shoulder range of motion than placebo, in patients with chronic tears who were treated with an exercise program [88]. Opposing results were found when an ultrasound-guided PRP injection was compared with dry needling in rotator cuff disease [89]. PRP led to a progressive reduction in pain and disability at six months after treatment in comparison to control [89]. Encouraging results for the potential of PRP to heal the muscle-tendon unit of the cuff at the level of degenerative tissue in refractory rotator cuff tendinopathy was also supported by data that intra-lesional injection of PRP resulted in improved functional and MRI outcome [90].

Platelet related growth factors has been shown *in vitro* to enhance chondrocyte proliferation, proteoglycan synthesis, collagen synthesis, and promotes chondrogenesis [91 - 94]. Despite this knowledge, that there are no clinical studies reporting outcomes for shoulder osteoarthritis. Recently, a technique for the treatment of focal chondral lesions at the glenohumeral joint with a combination of micronized allogeneic cartilage and platelet-rich plasma was described [95]. An increasing number of animal and clinical studies showed promising findings of the use of PRP in the knee and other joints [96 - 100]. Regarding other shoulder disorders, an interesting clinical report demonstrated that several cytokines are involved in the pathophysiology of synovial hyperplasia and capsular fibrosis detected in patient with adhesive capsulitis [101]. Additional research would provide better understanding of the exact mechanism of action of biological factors in the glenohumeral disorders, which is necessary to support whether PRP has any role in shoulder osteoarthritis treatment.

In summary, it is difficult to reach safe conclusions regarding the benefits from using of PRP in management of rotator cuff disorders due to the conflicting clinical evidence. Despite the encouraging *in vitro* results, the outcomes from clinical trials did not confirm the beneficial effect of PRP. The different surgical techniques, the different rehabilitation protocols, and most importantly, the different types of PRP seem to play an important role in outcome. Detailed research is important to clarify composition, effective dosage, and mode of action for PRPs [102]. Additional randomized multidisciplinary clinical trials are also needed to determine the effectiveness and clarify whether PRP application in rotator cuff tears and other glenohumeral disorders is beneficial or not.

GROWTH FACTORS

Apart from the growth factors that are released from PRP and have been discussed previously, several growth factors have been evaluated independently for their potential contribution to shoulder disorders healing. In general, growth factors are signal molecules that participate in the events of cell proliferation, protein synthesis, and as modulators of various phases of inflammation [103, 104]. They can be produced from various types of cells, such as inflammatory cells, platelets, and fibroblasts and their effectiveness depends on binding to specific receptors [103]. Due to their anabolic role, various growth factors are released to promote cellular proliferation and matrix deposition in early stages of tendon healing [43, 105]. Interestingly, growth factors initially appear at the proximal site of the myotendinous insertion and significantly earlier than at the distal site [43]. An absence at an early stage may be associated with underperfusion of the critical zone [43].

The main growth factors associated with shoulder disorders are the following: a) basic fibroblast growth factor (bFGF), b) platelet derived growth factor (PDGF), c) insulin-like growth factor-1 (IGF-1) d) transforming growth factor-beta (TGF-β), e) vascular endothelial growth factor (VEGF) and f) bone morphogenetic proteins 2, 7, 12, 13, 14 (BMP-2,7,12,13,14) [27, 88, 106]. bFGF is considered decisive in the proliferation and remodeling phases as potential stimulator of angiogenesis and fibroblast proliferation [43, 102, 106, 107]. PDGF plays an important role in early stages of healing process by stimulating and regulating the synthesis of IGF-1 and TGF-β [43, 102, 103, 106, 108]. IGF-1 and TGF-β are both released in the early phase of healing and they stimulate proliferation and migration of fibroblasts and other local cells [43, 106 - 108]. They also have a key role in chondrocyte proliferation and homeostasis [109, 110].

VEGF acts as a stimulator of angiogenesis of epi- and intratendinous vessels being present during inflammation, proliferation, and remodeling phase of healing process. In addition, it stimulates the secretion of bFGF [103, 107, 108]. BMPs are multifunctional cytokines, which are members of the transforming growth factor-β superfamily. They are regarded as factors that induce signal transduction for stem cell differentiation into osteoblastic cell [111, 112].

In Vitro

Several *in vitro* studies were performed to analyze the effect of these biologic factors on shoulder disorders, inspired by their participation in the tendon-bone healing process. bFGF was demonstrated having a stimulatory effect on the proliferation of rotator cuff tendon cells in a dose-dependent way, while simultaneously it suppressed secretion of collagen type I and type III [113]. Genetical modification of tenocytes with VEGF gene demonstrated very limited effects on the promotion of collagen production in an *in vitro* model [114]. BMP-2 and BMP-7 have shown in an *in vitro* model to increase collagen type I production and expression on tenocytes-like cells [115]. In parallel it was observed that BMP-7 increased cell activity [115]. A combination of bone marrow stromal cells (BMSCs) and growth and differentiation factor-5 (GDF-5) was shown to promote tendon healing, while treatment using either growth factor alone was unsuccessful. Administration of GDF-5 in muscle-derived stem cell implantation in an *in vitro* tendon healing appeared to improve the outcome of tendon repair [116]. Furthermore, sustained release of granulocyte-colony stimulating factor (G-CSF) ensured *via* the use of vesicular phospholipid gels (VPGs) showed some promising findings *in vitro* [117]. More recent data, identified gene expression as a new potential direction, as demonstrated by an *in vitro* study that identified sry-type homeobox protein-9 (SOX-9) and regulator of G-protein signaling-10 (RGS-10) as targets for gene therapy [118].

In Vivo

bFGF

An *in vivo* canine model revealed that bFGF accelerated the cell-proliferation phase of tendon healing, while simultaneously it promoted neovascularization and inflammation in the earliest phases following the suturing of the tendon [119]. However there was no enhancement in mechanical and functional properties of the repair [119]. Moreover, two different *in vivo* rat studies from a single group [102, 103] found that local application of bFGF accelerated the tendon-bone remodeling process of rotator cuff tendon defects reconstructed with acellular dermal matrix grafts [120, 121].

PDGF

In an *in vivo* sheep study, recombinant human PDGF-BB FiberWire (Arthrex, North Naples, FL, USA) when used to coat sutures that were used for rotator cuff tendon-bone repair, demonstrated enhanced healing histologically, but ultimate load to failure was no different to standard suture repairs [122]. In an analogous study an interpositional graft consisting of recombinant human PDGF-BB and a type I collagen matrix was implanted in an ovine model of rotator cuff repair [123]. After 12 weeks, it was found that this combination of PDGF-BB with a type I collagen matrix had the potential to augment surgical repair of rotator cuff tears [123]. Restoration of normal crimp patterning and collagen-bundle alignment in a rat rotator cuff repair model after delivery of cells expressing PDGF-BB on a polyglycolic acid scaffold was also suggested [124]. A significant increase in collagen and DNA synthesis in PDGF-b induced tendon fibroblasts was demonstrated in the same model [47].

IGF-1

Regarding IGF-1, using fibroblasts from rat tendons that were cultured and transferred with the gene of IGF-1, found that maximum load to failure and toughness were improved in the tendon repairs [47]. In an *in vivo* model, IGF-1 reached a peak expression in the early phase of supraspinatus tendon healing, earlier compared to bFGF and PDGF, indicating its involvement at the early phase of tendon healing [43].

TGF-β

Concerning the growth factor TGF-β, delivery of TGF-β3 with a heparin/fibrin-based TGF-β3 delivery system to the tendon-to-bone insertion in a rat model accelerated the healing process of supraspinatus tendon with enhanced vascularity, cellularity, inflammation, and cell proliferation at early stages [125]. Considerable improvements were also observed in structural properties at 28 days and in material properties at 56 days as compared to the controls [125].

Another relevant *in vivo* animal study investigated the delivery to the tendon-to-bone interface of repaired rat supraspinatus tendons of TGF-β3 in an injectable calcium-phosphate (Ca-P) matrix [126]. It was observed that the augmentation with the osteoconductive Ca-P matrix at the tendon-bone repair site was associated with new bone formation, increased fibrocartilage, improved collagen organization, and increased collagen type I/type III ratio at the healing tendon-to-bone interface in the early postoperative period after rotator cuff repair [126]. Plus, the addition of TGF-β3 significantly improved strength of the repair at 4 weeks postoperatively, which implied more mature healing [126]. On the contrary, TGF-β1 was suggested that over-activates inflammatory response and lead to scar formation [127]. In an animal flexor tendon repair study, the use of neutralizing antibodies against TGF-β1 could reverse this effect [127]. Examining the exact role of TGF-β1 and TGF-β3 at the tendon-to-bone insertion of repaired rat supraspinatus tendons by using an osmotic pump delivery system revealed that TGF-β1 increased type III collagen production, which was consistent with a scar-mediated healing response of low quality, but at the same time TGF-β3 application did not show improvement in healing [128].

VEGF

VEGF is among the growth factors contained in PRP, and therefore certain aspect of its actions has been described earlier. Solely, VEGF was demonstrated to be expressed in the early phase after tendon injury [129]. Due to its role in angiogenesis, it was proposed that it plays a critical role in tendon healing [130]. Recently, an *in vivo* model of rotator cuff healing showed that VEGF improved biomechanical properties of repaired tissue [131]. However, in two clinical studies, VEGF expression was associated with motion pain and synovial proliferation in patients with impingement syndrome, while a correlation with diabetes was also reported [132, 133].

BMPs

With reference to BMPs, supraspinatus tendon repairs treated with BMP-2 in a rat model were significantly stronger than the controlled group and histological analysis showed more organized healing after 4 and 6 weeks [51]. Similar results were presented when the effect of injectable hydrogel with BMP-2 on rotator cuff repair in rabbits was examined [134]. BMP-2 provided a powerful inductive ability between the tendon and the bone and enhanced tendon-bone healing through the neo-formation of fibrocartilage [134]. Beneficial results were also reported in a sheep animal study where delivery of recombinant human BMP-12 in a collagen or hyaluronan sponge resulted in accelerated healing of acute full-thickness rotator cuff repairs [135]. Contrarily, the application of mesenchymal stem cells genetically modified to over-express BMP-13 in a supraspinatus tendon-bone repair did not enhance healing, which suggests that further research is required in order to clarify the effect of BMP family [136].

Combination of Growth Factors

Apart from the research directly related to PRP, to our knowledge, there is only one *in vivo* study in the literature that investigated the effect of combining several different growth factors in shoulder disorders [137]. In this study, several growth factors from cortical bone extract (BMP-2 to BMP-7, TGF-β1, TGF-β2 TGF-β3 and FGF) were implanted with a type I collagen sponge into a healing supraspinatus repair of 72 sheep [137]. It was observed that the combination of growth factors resulted in formation of new bone, fibrocartilage, and soft tissue, with a parallel improvement of biomechanical properties at the repair site. Interestingly, further analysis implied that scar tissue formation might have occurred rather than tissue regeneration [137]. Considering the contradictory outcomes also seen with PRP application, which represents a mixture of different growth factors, as well as the complexity in growth factor interactions, it is recognizable that the different growth factors may have interrelating, synergistic, or sometimes antagonistic roles in tissue repair [43, 109, 137]. The exact mechanism of action of growth factors in musculoskeletal tissues needs to be further explored, as its exploration will serve as the basis for additional clinical applications.

STEM CELLS

In the last decade, the use of mesenchymal stem cells (MSCs) to enhance rotator cuff tendon healing and to manage musculoskeletal shoulder disorders has gain ground, due to their potential to differentiate towards different target cells and their anti-inflammatory and angiogenic characteristics [104, 138]. Stem cells, either embryonic or adult stems cells, are undifferentiated cells that under the influence of endogenous and exogenous factors have the potential to differentiate into certain adult cell types of mesenchymal origin (*i.e.*, bone, fat, tendon, muscle, cartilage) with various applications in tissue engineering and orthopedic surgery [139 - 142]. According to the tissue sources, the main types of adult MSCs are: a) Bone marrow-derived MSCs (BM-MSCs), b) Tenocyte-derived MSCs (T-MSCs), c) Adipose-

derived MSCs (A-MSCs), d) Muscle-derived MSCs (M-MSCs). Recently, additional sources of MSCs have been identified such as the synovia, periosteum, dermis, and peripheral blood, thus, further increasing the potential of future clinical applications [104, 141, 143].

Especially for rotator cuff healing, the main source of MSCs is the bone marrow, which can be easily accessed through aspiration even from the iliac crest, or from the proximal humerus [138 - 140]. These BM-MSCs after cultivation have the potential under suitable stimulation (*e.g.* insulin) to differentiate to tendon cells [138, 139, 144]. T-MSCs can be isolated from the supraspinatus or from the biceps tendon and are considered of extreme interest for rotator cuff repair enhancement [145, 146]. A-MSCs might be easy to be obtained, but their ability to differentiate is obviously reduced as compared to BM-MSCs [147]. In terms of other potential sources of MSCs, synovial cells were recently isolated from the subacromial bursa and glenohumeral joint, and they are considered as a good source of MSCs with a high potential for applications [148, 149].

Despite the apparent similar biological potential of different types of MSCs, several *in vivo* animal and clinical studies have explored the effect of different forms of MSCs on shoulder cuff disorders. In all the executed animal studies, MSCs were applied directly to the healing site or were delivered on an appropriate carrier matrix, which functioned as a scaffold as it can be realized below. In the first reported case control animal study, in 80 rats that were operated for supraspinatus tendon repair BM-MSCs isolated from rats` long bones were injected on the repair side. Despite their presence at the repair site, BM-MSCs were not proven to improve structural biomechanical aspects of healing [48]. In an attempt to address this inefficiency, additional differentiation factors may need to be combined with BM-MSCs therapy, attributing the inability to improve healing to poor signaling that did not induce differentiation of transplanted cells [48]. Indeed, in a subsequent series of studies, a) genetic modification of MSCs to over-express the developmental gene membrane type 1 matrix metalloproteinase (MT1-MMP), increased both structural and material biomechanical properties and increased the amount of fibrocartilage at the tendon-to-bone interface [150], b) MSCs genetically modified with scleraxis, a transcription factor believed to direct the tendinous attachments to bone, improved histological cartilage formation at the insertion site, with analogous enhancement of biomechanical properties [151], c) contrarily, MSCs genetically modified to over-express BMP-13 was not successful to enhance healing in a rat model of rotator cuff repair [136]. Thus, further enhancement of MSC differentiation seems to be critical, while a multi-factorial approach is more likely to induce appropriate healing and regeneration [136, 150, 151].

In an animal model, additional drilling to the greater tuberosity during the rotator cuff repair process was suggested that allowed BM-MSCs to migrate into the suture zone, and to infiltrate the site of rotator cuff repair, contributing to early postoperative rotator cuff healing [152]. Furthermore, a polyglycolic acid sheet scaffold with seeded BM-MSCs enhanced the expression of type I collagen and increased the mechanical strength of a regenerated rotator cuff tendon in a rabbit model [153]. Favorable results regarding the survival of MSCs were shown when these cells were encapsulated and implanted in open-cell polylactic acid scaffold in acute rabbit rotator cuff defect [154].

Regarding the other types of stem cells, local administration of A-MSCs indicated their potential to improve muscle function and tendon healing and decrease fatty infiltration after cuff repair [155]. In addition, the injection of highly purified muscle derived cells (MDCs) into the supraspinatus tendon of rats resulted in the engraftment of transplanted cells with morphology similar to resident tendon fibers [156]. However it was unclear whether MDCs had the capability to improve rotator cuff healing [156]. Finally, tendon stem/progenitor cells (TSPCs) that were isolated from human fetal Achilles tendon, cultured, and subsequently implanted in a rabbit rotator cuff defect, not only enhanced tendon regeneration by differentiating into tenocytes, but also prevent immunological rejection by secreting anti-inflammatory cytokines [157].

Despite the extensive research in animal experimental studies in reference to the role of MSCs in shoulder cuff healing, with rather promising results, there are only few clinical studies that evaluate the safety of clinical application of stem cells in rotator cuff tears. In a clinical study, 14 patients with complete rotator cuff tears were repaired with sutures and the repair was augmented with mononuclear stem cells from iliac crest bone marrow [158]. After one-year follow-up, in all patients tears showed integrity according to MRI criteria and 13 out of 14 patients had improved clinical outcome [158]. Recently, long term results of bone marrow-derived MSCs used as an adjunct to single-row rotator cuff repair at the time of arthroscopy were reported [159]. At 10 year follow up, re-tear of rotator cuff was found in only 13% of the MSC-treated group, *versus* 56% re-tear rate of the control group, indicating enhancement of healing from MSCs and durability of the clinical outcome [159]. Finally, two separate case reports that describe the treatment of rotator cuff tear with the use of a dermal allograft with the addition of MSCs and PRP also report favored outcome [160, 161].

In conclusion, the literature in respect to the effect of stem cells on shoulder disorders and their ability to facilitate regeneration of normal tendon-to-bone insertion and restrain growth of scar tissue is limited to almost only animal studies. Promising data are seen recently from the relevant clinical studies. However, further basic research is required in order to better understand differentiation potential and the relationship between MSCs with other biologic and signaling factors. Additional clinical research should be performed with randomized controlled trials to verify the encouraging results of experimental studies on humans.

OTHER FACTORS

The role of matrix metalloproteinases (MMPs) and their natural inhibitors known as tissue inhibitors of metalloproteinase (TIMPs) as potential biologic tools in rotator cuff tendon-bone healing is also under investigation over the last years. MMPs have the ability to shape connective tissue and to degrade collagen and elastin of the extracellular matrix (ECM), which is substantial for healing process of tendons [162] Imbalance in the equilibrium between MMPs and TIMPs in rotator cuff tendons, results in elevated levels of MMPs which can lead to degenerative rotator cuff tissue and cause tendon tears [162]. Further, it has been found that there was an increase in expression of MMP-1, MMP-2, and MMP-3 in rotator cuff tears, which appeared to influence the healing process [163 - 167]. Doxycycline was used to inhibit MMP-3 activity during rotator cuff healing in an animal study; the authors observed that inhibition of MMP led to improved biomechanical quality of the scar tissue as regards to increased load to failure, and better collagen fiber organization, which may offer a novel biological pathway to augment tendon-bone healing [168].

The use of scaffolds to mechanically stabilize the repair site has also been an area of active research. Natural and synthetic extracellular matrix (ECM) scaffolds have been used in order to share load as well as to provide a conductive chemical and/or structural environment for repair healing and remodeling [169 - 171]. Synthetic scaffolds have the advantage of being acellular and therefore do not induce a tissue response. Natural ECM needs intensive processing so as to remove cells and cell remnants that may cause intense tissue reactions. There are numerous questions related to their indication, surgical application, safety, mechanism of action, and efficacy that remain to be clarified or addressed, and other alternatives *via* scaffold-less approach may be worth exploring [172, 173].

Other biologic factors that might offer promising results in acceleration tendon-bone healing are the human growth hormone and proteoglycans [174, 175]. Nevertheless, there is still a long way for the scientific community to investigate the effectiveness of these factors in shoulder tendinopathy by animal studies and clinical trials. Finally, new horizons have opened up with the development of gene therapy and transgenic therapy, as described above in some examples. However the safety of these biological approaches for human trials needs to be addressed in future studies [104].

CONCLUSION

Increased morbidity of shoulder disorders led to an increased interest in the potential effect of biologic factors to improve cuff tendon healing or prevent cartilage degeneration. Despite the promising results of PRP in animal studies regarding augmentation of cuff tendon due to activation and release of growth factors, clinical trials have not confirmed their beneficial effect. Due to the continued challenges in clinical practice, the application of different growth factors and mesenchymal stem cells appears as promising alternatives for enhancing biologic repair. Despite promising outcomes reported in both *in vitro* and *in vivo* studies, data from clinical studies are still limited. Thus, future well-designed basic science studies are needed to improve understanding of the repair process in cellular and molecular level, but also, appropriately designed clinical trials are of paramount importance to elucidate the effectiveness of biologic factors in the management of shoulder disorders.

LIST OF ABBREVIATIONS

A-MSCs	=	Adipose-derived Mesenchymal Stem Cells.
bFGF	=	basic Fibroblast Growth Factor.
BM-MSCs	=	Bone Marrow-Derived Mesenchymal Stem Cells.
BMP	=	Bone Morphogenetic Proteins.
BMSCs	=	Bone Marrow Stromal Cells.
Ca-P	=	Calcium-Phosphate.

ECM	=	Elastin of the Extracellular Matrix.
G-CSF	=	Granulocyte-Colony Stimulating Factor.
GDF-5	=	Growth and Differentiation Factor-5.
IGF-1	=	Insulin-like Growth Factor 1.
L-PRF	=	Leukocyte-and Platelet-Rich Fibrin.
L-PRP	=	Leukocyte-and Platelet-Rich Plasma.
MDCs	=	Muscle Derived Cells.
MMP	=	Matrix MetalloProteinases.
M-MSCs	=	Muscle-derived Mesenchymal Stem Cells.
MSC	=	Mesenchymal Stem Cells.
MT1-MMP	=	Membrane Type 1 Matrix Metalloproteinase.
OA	=	Osteoarthritis.
PDGF	=	Platelet-Derived Growth Factor.
P-PRF	=	Pure Platelet-Rich Fibrin.
P-PRP	=	Pure Platelet-Rich Plasma.
PRP	=	Platelet-Rich Plasma.
PRPFM	=	Platelet-Rich Plasma Fibrin Matrix.
RC	=	Rotator Cuff.
RGS-10	=	Regulator of G-protein Signaling-10.
SOX-9	=	Sry-Type Homeobox Protein-9.
TGFb	=	Transforming Growth Factor-beta.
TIMPs	=	Tissue Inhibitors of Metalloproteinase.
T-MSCs	=	Tenocyte-derived Mesenchymal Stem Cells.
TSPCs	=	Tendon Stem/Progenitor Cells.
VEGF	=	Vascular Endothelial Growth Factor.
VPGs	=	Vesicular Phospholipid Gels.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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REFERENCES

[1] Urwin M, Symmons D, Allison T, *et al.* Estimating the burden of musculoskeletal disorders in the community: the comparative prevalence of symptoms at different anatomical sites, and the relation to social deprivation. Ann Rheum Dis 1998; 57(11): 649-55. [http://dx.doi.org/10.1136/ard.57.11.649] [PMID: 9924205]

[2] Shin KM. Partial-thickness rotator cuff tears. Korean J Pain 2011; 24(2): 69-73. [http://dx.doi.org/10.3344/kjp.2011.24.2.69] [PMID: 21716613]

[3] Bongers PM. The cost of shoulder pain at work. BMJ 2001; 322(7278): 64-5. [http://dx.doi.org/10.1136/bmj.322.7278.64] [PMID: 11154606]

[4] Mitchell C, Adebajo A, Hay E, Carr A. Shoulder pain: diagnosis and management in primary care. BMJ 2005; 331(7525): 1124-8. [http://dx.doi.org/10.1136/bmj.331.7525.1124] [PMID: 16282408]

[5] Sher JS, Uribe JW, Posada A, Murphy BJ, Zlatkin MB. Abnormal findings on magnetic resonance images of asymptomatic shoulders. J Bone Joint Surg Am 1995; 77(1): 10-5. [http://dx.doi.org/10.2106/00004623-199501000-00002] [PMID: 7822341]

[6] van Saase JL, van Romunde LK, Cats A, Vandenbroucke JP, Valkenburg HA. Epidemiology of osteoarthritis: Zoetermeer survey. Comparison of radiological osteoarthritis in a Dutch population with that in 10 other populations. Ann Rheum Dis 1989; 48(4): 271-80. [http://dx.doi.org/10.1136/ard.48.4.271] [PMID: 2712610]

[7] Petersson IF, Jacobsson LT. Osteoarthritis of the peripheral joints. Best Pract Res Clin Rheumatol 2002; 16(5): 741-60. [http://dx.doi.org/10.1053/berh.2002.0266] [PMID: 12473271]

[8] Killian ML, Cavinatto L, Galatz LM, Thomopoulos S. Recent advances in shoulder research. Arthritis Res Ther 2012; 14(3): 214. [PMID: 22709417]

[9] Kim SH, Wise BL, Zhang Y, Szabo RM. Increasing incidence of shoulder arthroplasty in the United States. J Bone Joint Surg Am 2011; 93(24): 2249-54. [http://dx.doi.org/10.2106/JBJS.J.01994] [PMID: 22258770]

[10] Gobezie R, Lenarz CJ, Wanner JP, Streit JJ. All-arthroscopic biologic total shoulder resurfacing. Arthroscopy 2011; 27(11): 1588-93. [http://dx.doi.org/10.1016/j.arthro.2011.07.008] [PMID: 21958671]

[11] Walch G, Boileau P. Prosthetic adaptability: a new concept for shoulder arthroplasty. J Shoulder Elbow Surg 1999; 8(5): 443-51. [http://dx.doi.org/10.1016/S1058-2746(99)90074-5] [PMID: 10543597]

[12] Nimbarte AD, Sun Y, Jaridi M, Hsiao H. Biomechanical loading of the shoulder complex and lumbosacral joints during dynamic cart pushing task. Appl Ergon 2013; 44(5): 841-9. [http://dx.doi.org/10.1016/j.apergo.2013.02.008] [PMID: 23566675]

[13] van der Helm FC. Analysis of the kinematic and dynamic behavior of the shoulder mechanism. J Biomech 1994; 27(5): 527-50. [http://dx.doi.org/10.1016/0021-9290(94)90064-7] [PMID: 8027089]

[14] Neer CS II. Anterior acromioplasty for the chronic impingement syndrome in the shoulder: a preliminary report. J Bone Joint Surg Am 1972; 54(1): 41-50. [http://dx.doi.org/10.2106/00004623-197254010-00003] [PMID: 5054450]

[15] McMaster WC, Troup J. A survey of interfering shoulder pain in United States competitive swimmers. Am J Sports Med 1993; 21(1): 67-70. [http://dx.doi.org/10.1177/036354659302100112] [PMID: 8427371]

[16] Wendelboe AM, Hegmann KT, Gren LH, Alder SC, White GL Jr, Lyon JL. Associations between body-mass index and surgery for rotator cuff tendinitis. J Bone Joint Surg Am 2004; 86-A(4): 743-7. [http://dx.doi.org/10.2106/00004623-200404000-00011] [PMID: 15069138]

[17] Lohr JF, Uhthoff HK. The microvascular pattern of the supraspinatus tendon. Clin Orthop Relat Res 1990; (254): 35-8. [PMID: 2323147]

[18] Yadav H, Nho S, Romeo A, MacGillivray JD. Rotator cuff tears: pathology and repair. Knee Surg Sports Traumatol Arthrosc 2009; 17(4): 409-21. [http://dx.doi.org/10.1007/s00167-008-0686-8] [PMID: 19104772]

[19] 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. [http://dx.doi.org/10.1302/0301-620X.92B3.23074] [PMID: 20190320]

[20] Via AG, De Cupis M, Spoliti M, Oliva F. Clinical and biological aspects of rotator cuff tears. Muscles Ligaments Tendons J 2013; 3(2): 70-9. [PMID: 23888289]

[21] Chopp JN, ONeill JM, Hurley K, Dickerson CR. Superior humeral head migration occurs after a protocol designed to fatigue the rotator cuff: a radiographic analysis. J Shoulder Elbow Surg 2010; 19(8): 1137-44. [http://dx.doi.org/10.1016/j.jse.2010.03.017] [PMID: 20598916]

[22] Lapner PC, Su Y, Simon D, El-Fatori S, Lopez-Vidriero E. Does the upward migration index predict function and quality of life in arthroscopic rotator cuff repair? Clin Orthop Relat Res 2010; 468(11): 3063-9. [http://dx.doi.org/10.1007/s11999-010-1457-7] [PMID: 20607465]

[23] Elser F, Braun S, Dewing CB, Millett PJ. Glenohumeral joint preservation: current options for managing articular cartilage lesions in young, active patients. Arthroscopy 2010; 26(5): 685-96. [http://dx.doi.org/10.1016/j.arthro.2009.10.017] [PMID: 20434669]

[24] Brophy RH, Marx RG. Osteoarthritis following shoulder instability. Clin Sports Med 2005; 24(1): 47-56. [http://dx.doi.org/10.1016/j.csm.2004.08.010] [PMID: 15636776]

[25] Borrelli J Jr, Silva MJ, Zaegel MA, Franz C, Sandell LJ. Single high-energy impact load causes posttraumatic OA in young rabbits *via* a decrease in cellular metabolism. J Orthop Res 2009; 27(3): 347-52. [http://dx.doi.org/10.1002/jor.20760] [PMID: 18924142]

[26] Cruess RL. Experience with steroid-induced avascular necrosis of the shoulder and etiologic considerations regarding osteonecrosis of the hip. Clin Orthop Relat Res 1978; (130): 86-93. [PMID: 639411]

[27] 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. [http://dx.doi.org/10.2106/00004623-200402000-00002] [PMID: 14960664]

[28] Huijsmans PE, Pritchard MP, Berghs BM, van Rooyen KS, Wallace AL, de Beer JF. Arthroscopic rotator cuff repair with double-row fixation. J Bone Joint Surg Am 2007; 89(6): 1248-57. [http://dx.doi.org/10.2106/00004623-200706000-00013] [PMID: 17545428]

[29] 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.
[http://dx.doi.org/10.1016/j.jse.2005.09.017] [PMID: 16679227]

[30] Sugaya H, Maeda K, Matsuki K, Moriishi J. Repair integrity and functional outcome after arthroscopic double-row rotator cuff repair. A prospective outcome study. J Bone Joint Surg Am 2007; 89(5): 953-60.
[PMID: 17473131]

[31] Liem D, Bartl C, Lichtenberg S, Magosch P, Habermeyer P. Clinical outcome and tendon integrity of arthroscopic *versus* mini-open supraspinatus tendon repair: a magnetic resonance imaging-controlled matched-pair analysis. Arthroscopy 2007; 23(5): 514-21.
[http://dx.doi.org/10.1016/j.arthro.2006.12.028] [PMID: 17478283]

[32] Duquin TR, Buyea C, Bisson LJ. Which method of rotator cuff repair leads to the highest rate of structural healing? A systematic review. Am J Sports Med 2010; 38(4): 835-41.
[http://dx.doi.org/10.1177/0363546509359679] [PMID: 20357403]

[33] Abtahi AM, Granger EK, Tashjian RZ. Factors affecting healing after arthroscopic rotator cuff repair. World J Orthop 2015; 6(2): 211-20.
[http://dx.doi.org/10.5312/wjo.v6.i2.211] [PMID: 25793161]

[34] Lundgreen K, Lian OB, Scott A, Nassab P, Fearon A, Engebretsen L. Rotator cuff tear degeneration and cell apoptosis in smokers *versus* nonsmokers. Arthroscopy 2014; 30(8): 936-41.
[http://dx.doi.org/10.1016/j.arthro.2014.03.027] [PMID: 24863404]

[35] Mallon WJ, Misamore G, Snead DS, Denton P. The impact of preoperative smoking habits on the results of rotator cuff repair. J Shoulder Elbow Surg 2004; 13(2): 129-32.
[http://dx.doi.org/10.1016/j.jse.2003.11.002] [PMID: 14997086]

[36] Mall NA, Tanaka MJ, Choi LS, Paletta GA Jr. Factors affecting rotator cuff healing. J Bone Joint Surg Am 2014; 96(9): 778-88.
[http://dx.doi.org/10.2106/JBJS.M.00583] [PMID: 24806015]

[37] Grimberg J, Diop A, Kalra K, Charousset C, Duranthon LD, Maurel N. *In vitro* biomechanical comparison of three different types of single- and double-row arthroscopic rotator cuff repairs: analysis of continuous bone-tendon contact pressure and surface during different simulated joint positions. J Shoulder Elbow Surg 2010; 19(2): 236-43.
[http://dx.doi.org/10.1016/j.jse.2009.09.006] [PMID: 19995682]

[38] Accousti KJ, Flatow EL. Technical pearls on how to maximize healing of the rotator cuff. Instr Course Lect 2007; 56: 3-12.
[PMID: 17472287]

[39] Benson RT, McDonnell SM, Rees JL, Athanasou NA, Carr AJ. The morphological and immunocytochemical features of impingement syndrome and partial-thickness rotator-cuff tear in relation to outcome after subacromial decompression. J Bone Joint Surg Br 2009; 91(1): 119-23.
[http://dx.doi.org/10.1302/0301-620X.91B1.21058] [PMID: 19092016]

[40] Cole AS, Cordiner-Lawrie S, Carr AJ, Athanasou NA. Localised deposition of amyloid in tears of the rotator cuff. J Bone Joint Surg Br 2001; 83(4): 561-4.
[http://dx.doi.org/10.1302/0301-620X.83B4.11547] [PMID: 11380132]

[41] de Mos M, van der Windt AE, Jahr H, *et al.* Can platelet-rich plasma enhance tendon repair? A cell culture study. Am J Sports Med 2008; 36(6): 1171-8.
[http://dx.doi.org/10.1177/0363546508314430] [PMID: 18326832]

[42] Cummins CA, Murrell GA. Mode of failure for rotator cuff repair with suture anchors identified at revision surgery. J Shoulder Elbow Surg 2003; 12(2): 128-33.
[http://dx.doi.org/10.1067/mse.2003.21] [PMID: 12700563]

[43] Kobayashi M, Itoi E, Minagawa H, *et al.* Expression of growth factors in the early phase of supraspinatus tendon healing in rabbits. J Shoulder Elbow Surg 2006; 15(3): 371-7.
[http://dx.doi.org/10.1016/j.jse.2005.09.003] [PMID: 16679241]

[44] Galatz LM, Sandell LJ, Rothermich SY, *et al.* Characteristics of the rat supraspinatus tendon during tendon-to-bone healing after acute injury. J Orthop Res 2006; 24(3): 541-50.
[http://dx.doi.org/10.1002/jor.20067] [PMID: 16456829]

[45] Rodeo SA, Arnoczky SP, Torzilli PA, Hidaka C, Warren RF. Tendon-healing in a bone tunnel. A biomechanical and histological study in the dog. J Bone Joint Surg Am 1993; 75(12): 1795-803.
[http://dx.doi.org/10.2106/00004623-199312000-00009] [PMID: 8258550]

[46] Derwin KA, Baker AR, Iannotti JP, McCarron JA. Preclinical models for translating regenerative medicine therapies for rotator cuff repair. Tissue Eng Part B Rev 2010; 16(1): 21-30.
[http://dx.doi.org/10.1089/ten.teb.2009.0209] [PMID: 19663651]

[47] Dines JS, Grande DA, Dines DM. Tissue engineering and rotator cuff tendon healing. J Shoulder Elbow Surg 2007; 16(5)(Suppl.): S204-7.
[http://dx.doi.org/10.1016/j.jse.2007.03.004] [PMID: 17524676]

[48] Gulotta LV, Kovacevic D, Ehteshami JR, Dagher E, Packer JD, Rodeo SA. Application of bone marrow-derived mesenchymal stem cells in a rotator cuff repair model. Am J Sports Med 2009; 37(11): 2126-33.
[http://dx.doi.org/10.1177/0363546509339582] [PMID: 19684297]

[49] Isaac C, Gharaibeh B, Witt M, Wright VJ, Huard J. Biologic approaches to enhance rotator cuff healing after injury. J Shoulder Elbow Surg 2012; 21(2): 181-90.
[http://dx.doi.org/10.1016/j.jse.2011.10.004] [PMID: 22244061]

[50] Milano G, Saccomanno MF, Careri S, Taccardo G, De Vitis R, Fabbriciani C. Efficacy of marrow-stimulating technique in arthroscopic rotator cuff repair: a prospective randomized study. Arthroscopy 2013; 29(5): 802-10.
[http://dx.doi.org/10.1016/j.arthro.2013.01.019] [PMID: 23522987]

[51] Murray DH, Kubiak EN, Jazrawi LM, *et al.* The effect of cartilage-derived morphogenetic protein 2 on initial healing of a rotator cuff defect in a rat model. J Shoulder Elbow Surg 2007; 16(2): 251-4.
[http://dx.doi.org/10.1016/j.jse.2006.07.002] [PMID: 17113320]

[52] Rodeo SA. Biologic augmentation of rotator cuff tendon repair. J Shoulder Elbow Surg 2007; 16(5)(Suppl.): S191-7.
[http://dx.doi.org/10.1016/j.jse.2007.03.012] [PMID: 17574875]

[53] Randelli PS, Arrigoni P, Cabitza P, Volpi P, Maffulli N. Autologous platelet rich plasma for arthroscopic rotator cuff repair. A pilot study. Disabil Rehabil 2008; 30(20-22): 1584-9.
[http://dx.doi.org/10.1080/09638280801906081] [PMID: 18608363]

[54] Gamradt SC, Warren RF. Platelet rich plasma in rotator cuff repair. Tech Orthop 2007; 22(1): 26-33.
[http://dx.doi.org/10.1097/01.bto.0000261868.03232.dd]

[55] Maniscalco P, Gambera D, Lunati A, *et al.* The Cascade membrane: a new PRP device for tendon ruptures. Description and case report on rotator cuff tendon. Acta Biomed 2008; 79(3): 223-6.
[PMID: 19260383]

[56] Eppley BL, Woodell JE, Higgins J. Platelet quantification and growth factor analysis from platelet-rich plasma: implications for wound healing. Plast Reconstr Surg 2004; 114(6): 1502-8.
[http://dx.doi.org/10.1097/01.PRS.0000138251.07040.51] [PMID: 15509939]

[57] Mei-Dan O, Carmont MR. The role of platelet-rich plasma in rotator cuff repair. Sports Med Arthrosc Rev 2011; 19(3): 244-50.
[http://dx.doi.org/10.1097/JSA.0b013e318227b2dc] [PMID: 21822108]

[58] Dohan Ehrenfest DM, Andia I, Zumstein MA, Zhang CQ, Pinto NR, Bielecki T. Classification of platelet concentrates (Platelet-Rich Plasma-PRP, Platelet-Rich Fibrin-PRF) for topical and infiltrative use in orthopedic and sports medicine: current consensus, clinical implications and perspectives. Muscles Ligaments Tendons J 2014; 4(1): 3-9.
[PMID: 24932440]

[59] Bielecki T, Dohan Ehrenfest DM. Platelet-rich plasma (PRP) and Platelet-Rich Fibrin (PRF): surgical adjuvants, preparations for *in situ* regenerative medicine and tools for tissue engineering. Curr Pharm Biotechnol 2012; 13(7): 1121-30.
[http://dx.doi.org/10.2174/138920112800624292] [PMID: 21740380]

[60] Gulotta LV, Rodeo SA. Growth factors for rotator cuff repair. Clin Sports Med 2009; 28(1): 13-23.
[http://dx.doi.org/10.1016/j.csm.2008.09.002] [PMID: 19064162]

[61] Moraes VY, Lenza M, Tamaoki MJ, Faloppa F, Belloti JC. Platelet-rich therapies for musculoskeletal soft tissue injuries. Cochrane Database Syst Rev 2014; 4(4): CD010071.
[PMID: 24782334]

[62] Boswell SG, Cole BJ, Sundman EA, Karas V, Fortier LA. Platelet-rich plasma: a milieu of bioactive factors. Arthroscopy 2012; 28(3): 429-39.
[http://dx.doi.org/10.1016/j.arthro.2011.10.018] [PMID: 22284405]

[63] de Vos RJ, van Veldhoven PL, Moen MH, Weir A, Tol JL, Maffulli N. Autologous growth factor injections in chronic tendinopathy: a systematic review. Br Med Bull 2010; 95: 63-77.
[http://dx.doi.org/10.1093/bmb/ldq006] [PMID: 20197290]

[64] Martínez-Zapata MJ, Martí-Carvajal A, Solà I, *et al.* Efficacy and safety of the use of autologous plasma rich in platelets for tissue regeneration: a systematic review. Transfusion 2009; 49(1): 44-56.
[http://dx.doi.org/10.1111/j.1537-2995.2008.01945.x] [PMID: 18954394]

[65] Lopez-Vidriero E, Goulding KA, Simon DA, Sanchez M, Johnson DH. The use of platelet-rich plasma in arthroscopy and sports medicine: optimizing the healing environment. Arthroscopy 2010; 26(2): 269-78.
[http://dx.doi.org/10.1016/j.arthro.2009.11.015] [PMID: 20141991]

[66] 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.
[http://dx.doi.org/10.1016/j.tibtech.2008.11.009] [PMID: 19187989]

[67] Dohan Ehrenfest DM, Del Corso M, Diss A, Mouhyi J, Charrier JB. Three-dimensional architecture and cell composition of a Choukrouns platelet-rich fibrin clot and membrane. J Periodontol 2010; 81(4): 546-55.
[http://dx.doi.org/10.1902/jop.2009.090531] [PMID: 20373539]

[68] Matras H. Effect of various fibrin preparations on reimplantations in the rat skin. Osterr Z Stomatol 1970; 67(9): 338-59.
[PMID: 4917644]

[69] Kajikawa Y, Morihara T, Sakamoto H, *et al.* Platelet-rich plasma enhances the initial mobilization of circulation-derived cells for tendon healing. J Cell Physiol 2008; 215(3): 837-45.
[http://dx.doi.org/10.1002/jcp.21368] [PMID: 18181148]

[70] Hoppe S, Alini M, Benneker LM, Milz S, Boileau P, Zumstein MA. Tenocytes of chronic rotator cuff tendon tears can be stimulated by platelet-released growth factors. J Shoulder Elbow Surg 2013; 22(3): 340-9.
[http://dx.doi.org/10.1016/j.jse.2012.01.016] [PMID: 22521394]

[71] Jo CH, Kim JE, Yoon KS, Shin S. Platelet-rich plasma stimulates cell proliferation and enhances matrix gene expression and synthesis in tenocytes from human rotator cuff tendons with degenerative tears. Am J Sports Med 2012; 40(5): 1035-45.
[http://dx.doi.org/10.1177/0363546512437525] [PMID: 22366517]

[72] Chung SW, Song BW, Kim YH, Park KU, Oh JH. Effect of platelet-rich plasma and porcine dermal collagen graft augmentation for rotator cuff healing in a rabbit model. Am J Sports Med 2013; 41(12): 2909-18.
[http://dx.doi.org/10.1177/0363546513503810] [PMID: 24047553]

[73] Dolkart O, Chechik O, Zarfati Y, Brosh T, Alhajajra F, Maman E. A single dose of platelet-rich plasma improves the organization and strength of a surgically repaired rotator cuff tendon in rats. Arch Orthop Trauma Surg 2014; 134(9): 1271-7.
[http://dx.doi.org/10.1007/s00402-014-2026-4] [PMID: 25027676]

[74] Ersen A, Demirhan M, Atalar AC, Kapicioğlu M, Baysal G. Platelet-rich plasma for enhancing surgical rotator cuff repair: evaluation and comparison of two application methods in a rat model. Arch Orthop Trauma Surg 2014; 134(3): 405-11.
[http://dx.doi.org/10.1007/s00402-013-1914-3] [PMID: 24379006]

[75] Chahal J, Van Thiel GS, Mall N, *et al.* The role of platelet-rich plasma in arthroscopic rotator cuff repair: a systematic review with quantitative synthesis. Arthroscopy 2012; 28(11): 1718-27.
[http://dx.doi.org/10.1016/j.arthro.2012.03.007] [PMID: 22694941]

[76] Castricini R, Longo UG, De Benedetto M, *et al.* Platelet-rich plasma augmentation for arthroscopic rotator cuff repair: a randomized controlled trial. Am J Sports Med 2011; 39(2): 258-65.
[http://dx.doi.org/10.1177/0363546510390780] [PMID: 21160018]

[77] 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.
[http://dx.doi.org/10.1016/j.jse.2011.02.008] [PMID: 21570659]

[78] Jo CH, Kim JE, Yoon KS, *et al.* Does platelet-rich plasma accelerate recovery after rotator cuff repair? A prospective cohort study. Am J Sports Med 2011; 39(10): 2082-90.
[http://dx.doi.org/10.1177/0363546511413454] [PMID: 21737832]

[79] 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.
[http://dx.doi.org/10.1177/0363546511424402] [PMID: 22016459]

[80] Wang A, McCann P, Colliver J, *et al.* Do postoperative platelet-rich plasma injections accelerate early tendon healing and functional recovery after arthroscopic supraspinatus repair? A randomized controlled trial. Am J Sports Med 2015; 43(6): 1430-7.
[http://dx.doi.org/10.1177/0363546515572602] [PMID: 25790835]

[81] Malavolta EA, Gracitelli ME, Ferreira Neto AA, Assunção 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.
[http://dx.doi.org/10.1177/0363546514541777] [PMID: 25086065]

[82] Ruiz-Moneo P, Molano-Muñoz J, Prieto E, Algorta J. Plasma rich in growth factors in arthroscopic rotator cuff repair: a randomized, double-blind, controlled clinical trial. Arthroscopy 2013; 29(1): 2-9.
[http://dx.doi.org/10.1016/j.arthro.2012.08.014] [PMID: 23276410]

[83] 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, randomized clinical study. Am J Sports Med 2012; 40(6): 1234-41.
[http://dx.doi.org/10.1177/0363546512442924] [PMID: 22495146]

[84] Barber FA, Hrnack SA, Snyder SJ, Hapa O. Rotator cuff repair healing influenced by platelet-rich plasma construct augmentation. Arthroscopy 2011; 27(8): 1029-35.
[http://dx.doi.org/10.1016/j.arthro.2011.06.010] [PMID: 21802625]

[85] Gumina S, Campagna V, Ferrazza G, *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.
[http://dx.doi.org/10.2106/JBJS.K.00394] [PMID: 22854988]

[86] Jo CH, Shin JS, Lee YG, *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.
[http://dx.doi.org/10.1177/0363546513497925] [PMID: 23921338]

[87] Charousset C, Zaoui A, Bellaïche 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.
[http://dx.doi.org/10.1016/j.arthro.2013.12.018] [PMID: 24680303]

[88] Kesikburun S, Tan AK, Yilmaz B, Yaşar E, Yazicioğlu K. Platelet-rich plasma injections in the treatment of chronic rotator cuff tendinopathy: a randomized controlled trial with 1-year follow-up. Am J Sports Med 2013; 41(11): 2609-16.
[http://dx.doi.org/10.1177/0363546513496542] [PMID: 23893418]

[89] Rha DW, Park GY, Kim YK, Kim MT, Lee SC. Comparison of the therapeutic effects of ultrasound-guided platelet-rich plasma injection and dry needling in rotator cuff disease: a randomized controlled trial. Clin Rehabil 2013; 27(2): 113-22.
[http://dx.doi.org/10.1177/0269215512448388] [PMID: 23035005]

[90] Scarpone M, Rabago D, Snell E, *et al.* Effectiveness of platelet-rich plasma unjection for rotator cuff tendinopathy: A prospective open-label study. Glob Adv Health Med 2013; 2(2): 26-31.
[http://dx.doi.org/10.7453/gahmj.2012.054] [PMID: 24416661]

[91] Lohmann CH, Schwartz Z, Niederauer GG, Carnes DL Jr, Dean DD, Boyan BD. Pretreatment with platelet derived growth factor-BB modulates the ability of costochondral resting zone chondrocytes incorporated into PLA/PGA scaffolds to form new cartilage *in vivo*. Biomaterials 2000; 21(1): 49-61.
[http://dx.doi.org/10.1016/S0142-9612(99)00132-5] [PMID: 10619678]

[92] Akeda K, An HS, Okuma M, *et al.* Platelet-rich plasma stimulates porcine articular chondrocyte proliferation and matrix biosynthesis. Osteoarthritis Cartilage 2006; 14(12): 1272-80.
[http://dx.doi.org/10.1016/j.joca.2006.05.008] [PMID: 16820306]

[93] Weiser L, Bhargava M, Attia E, Torzilli PA. Effect of serum and platelet-derived growth factor on chondrocytes grown in collagen gels. Tissue Eng 1999; 5(6): 533-44.
[http://dx.doi.org/10.1089/ten.1999.5.533] [PMID: 10611545]

[94] Choi YC, Morris GM, Sokoloff L. Effect of platelet lysate on growth and sulfated glycosaminoglycan synthesis in articular chondrocyte cultures. Arthritis Rheum 1980; 23(2): 220-4.
[http://dx.doi.org/10.1002/art.1780230213] [PMID: 7362669]

[95] Shin JJ, Mellano C, Cvetanovich GL, Frank RM, Cole BJ. Treatment of glenoid chondral defect using micronized allogeneic cartilage matrix implantation. Arthrosc Tech 2014; 3(4): e519-22.
[http://dx.doi.org/10.1016/j.eats.2014.05.014] [PMID: 25264514]

[96] Kon E, Buda R, Filardo G, *et al.* Platelet-rich plasma: intra-articular knee injections produced favorable results on degenerative cartilage lesions. Knee Surg Sports Traumatol Arthrosc 2010; 18(4): 472-9.
[http://dx.doi.org/10.1007/s00167-009-0940-8] [PMID: 19838676]

[97] Gobbi A, Karnatzikos G, Mahajan V, Malchira S. Platelet-rich plasma treatment in symptomatic patients with knee osteoarthritis: preliminary results in a group of active patients. Sports Health 2012; 4(2): 162-72.
[http://dx.doi.org/10.1177/1941738111431801] [PMID: 23016084]

[98] Patel S, Dhillon MS, Aggarwal S, Marwaha N, Jain A. Treatment with platelet-rich plasma is more effective than placebo for knee osteoarthritis: a prospective, double-blind, randomized trial. Am J Sports Med 2013; 41(2): 356-64.
[http://dx.doi.org/10.1177/0363546512471299] [PMID: 23299850]

[99] Sampson S, Reed M, Silvers H, Meng M, Mandelbaum B. Injection of platelet-rich plasma in patients with primary and secondary knee osteoarthritis: a pilot study. Am J Phys Med Rehabil 2010; 89(12): 961-9.
[http://dx.doi.org/10.1097/PHM.0b013e3181fc7edf] [PMID: 21403592]

[100] Sun Y, Feng Y, Zhang CQ, Chen SB, Cheng XG. The regenerative effect of platelet-rich plasma on healing in large osteochondral defects. Int Orthop 2010; 34(4): 589-97.
[http://dx.doi.org/10.1007/s00264-009-0793-2] [PMID: 19434411]

[101] Rodeo SA, Hannafin JA, Tom J, Warren RF, Wickiewicz TL. Immunolocalization of cytokines and their receptors in adhesive capsulitis of the shoulder. J Orthop Res 1997; 15(3): 427-36.
[http://dx.doi.org/10.1002/jor.1100150316] [PMID: 9246090]

[102] Anitua E, Sanchez M, Orive G. The importance of understanding what is platelet-rich growth factor (PRGF) and what is not. J Shoulder Elbow Surg 2011; 20(1): e23-4.

[103] Molloy T, Wang Y, Murrell G. The roles of growth factors in tendon and ligament healing. Sports Med 2003; 33(5): 381-94.
[http://dx.doi.org/10.2165/00007256-200333050-00004] [PMID: 12696985]

[104] Nixon AJ, Watts AE, Schnabel LV. Cell- and gene-based approaches to tendon regeneration. J Shoulder Elbow Surg 2012; 21(2): 278-94.
[http://dx.doi.org/10.1016/j.jse.2011.11.015] [PMID: 22244071]

[105] Chang J, Most D, Stelnicki E, *et al.* Gene expression of transforming growth factor beta-1 in rabbit zone II flexor tendon wound healing: evidence for dual mechanisms of repair. Plast Reconstr Surg 1997; 100(4): 937-44.
[http://dx.doi.org/10.1097/00006534-199709001-00016] [PMID: 9290662]

[106] Würgler-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.): S198-203.
[http://dx.doi.org/10.1016/j.jse.2007.04.003] [PMID: 17903711]

[107] Hsu C, Chang J. Clinical implications of growth factors in flexor tendon wound healing. J Hand Surg Am 2004; 29(4): 551-63.
[http://dx.doi.org/10.1016/j.jhsa.2004.04.020] [PMID: 15249076]

[108] Schaer M, Schober M, Berger S, Boileau P, Zumstein MA. Biologically based strategies to augment rotator cuff tears. Int J Shoulder Surg 2012; 6(2): 51-60.
[http://dx.doi.org/10.4103/0973-6042.96995] [PMID: 22787334]

[109] Guerne PA, Sublet A, Lotz M. Growth factor responsiveness of human articular chondrocytes: distinct profiles in primary chondrocytes, subcultured chondrocytes, and fibroblasts. J Cell Physiol 1994; 158(3): 476-84.
[http://dx.doi.org/10.1002/jcp.1041580312] [PMID: 8126071]

[110] Longobardi L, ORear L, Aakula S, *et al.* Effect of IGF-I in the chondrogenesis of bone marrow mesenchymal stem cells in the presence or absence of TGF-beta signaling. J Bone Miner Res 2006; 21(4): 626-36.
[http://dx.doi.org/10.1359/jbmr.051213] [PMID: 16598383]

[111] Reddi AH, Cunningham NS. Bone induction by osteogenin and bone morphogenetic proteins. Biomaterials 1990; 11: 33-4.
[PMID: 2204436]

[112] Reddi AH. Bone morphogenetic proteins, bone marrow stromal cells, and mesenchymal stem cells. Maureen Owen revisited. Clin Orthop Relat Res 1995; (313): 115-9.
[PMID: 7641468]

[113] Takahashi S, Nakajima M, Kobayashi M, *et al.* Effect of recombinant basic fibroblast growth factor (bFGF) on fibroblast-like cells from human rotator cuff tendon. Tohoku J Exp Med 2002; 198(4): 207-14.
[http://dx.doi.org/10.1620/tjem.198.207] [PMID: 12630552]

[114] Wang XT, Liu PY, Tang JB. Tendon healing *in vitro*: modification of tenocytes with exogenous vascular endothelial growth factor gene increases expression of transforming growth factor beta but minimally affects expression of collagen genes. J Hand Surg Am 2005; 30(2): 222-9.
[http://dx.doi.org/10.1016/j.jhsa.2004.09.002] [PMID: 15781343]

[115] Pauly S, Klatte F, Strobel C, *et al.* BMP-2 and BMP-7 affect human rotator cuff tendon cells *in vitro*. J Shoulder Elbow Surg 2012; 21(4): 464-73.
[http://dx.doi.org/10.1016/j.jse.2011.01.015] [PMID: 21454098]

[116] Ozasa Y, Gingery A, Thoreson AR, An KN, Zhao C, Amadio PC. A comparative study of the effects of growth and differentiation factor 5 on muscle-derived stem cells and bone marrow stromal cells in an *in vitro* tendon healing model. J Hand Surg Am 2014; 39(9): 1706-13.
[http://dx.doi.org/10.1016/j.jhsa.2014.05.005] [PMID: 24909566]

[117] Buchmann S, Sandmann GH, Walz L, *et al.* Growth factor release by vesicular phospholipid gels: *in vitro* results and application for rotator cuff repair in a rat model. BMC Musculoskelet Disord 2015; 16: 82.
[http://dx.doi.org/10.1186/s12891-015-0542-1] [PMID: 25888096]

[118] Warnock JJ, Fox DB, Stoker AM, Cook JL. Evaluation of *in vitro* growth factor treatments on fibrochondrogenesis by synovial membrane cells from osteoarthritic and nonosteoarthritic joints of dogs. Am J Vet Res 2011; 72(4): 500-11.
[http://dx.doi.org/10.2460/ajvr.72.4.500] [PMID: 21453151]

[119] Thomopoulos S, Kim HM, Das R, *et al.* The effects of exogenous basic fibroblast growth factor on intrasynovial flexor tendon healing in a canine model. J Bone Joint Surg Am 2010; 92(13): 2285-93.
[http://dx.doi.org/10.2106/JBJS.I.01601] [PMID: 20926722]

[120] Ide J, Kikukawa K, Hirose J, Iyama K, Sakamoto H, Mizuta H. The effects of fibroblast growth factor-2 on rotator cuff reconstruction with acellular dermal matrix grafts. Arthroscopy 2009; 25(6): 608-16.
[http://dx.doi.org/10.1016/j.arthro.2008.11.011] [PMID: 19501290]

[121] Ide J, Kikukawa K, Hirose J, Iyama K, Sakamoto H, Mizuta H. Reconstruction of large rotator-cuff tears with acellular dermal matrix grafts in rats. J Shoulder Elbow Surg 2009; 18(2): 288-95.
[http://dx.doi.org/10.1016/j.jse.2008.09.004] [PMID: 19058978]

[122] Uggen C, Dines J, McGarry M, Grande D, Lee T, Limpisvasti O. The effect of recombinant human platelet-derived growth factor BB-coated sutures on rotator cuff healing in a sheep model. Arthroscopy 2010; 26(11): 1456-62.
[http://dx.doi.org/10.1016/j.arthro.2010.02.025] [PMID: 20729027]

[123] Hee CK, Dines JS, Dines DM, *et al.* Augmentation of a rotator cuff suture repair using rhPDGF-BB and a type I bovine collagen matrix in an ovine model. Am J Sports Med 2011; 39(8): 1630-9.
[http://dx.doi.org/10.1177/0363546511404942] [PMID: 21555508]

[124] Uggen JC, Dines J, Uggen CW, *et al.* Tendon gene therapy modulates the local repair environment in the shoulder. J Am Osteopath Assoc 2005; 105(1): 20-1.
[PMID: 15710662]

[125] 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.
[http://dx.doi.org/10.1002/jor.21301] [PMID: 21246611]

[126] Kovacevic D, Fox AJ, Bedi A, *et al.* Calcium-phosphate matrix with or without TGF-β3 improves tendon-bone healing after rotator cuff repair. Am J Sports Med 2011; 39(4): 811-9.
[http://dx.doi.org/10.1177/0363546511399378] [PMID: 21406666]

[127] Chang J, Thunder R, Most D, Longaker MT, Lineaweaver WC. Studies in flexor tendon wound healing: neutralizing antibody to TGF-beta1 increases postoperative range of motion. Plast Reconstr Surg 2000; 105(1): 148-55.
[http://dx.doi.org/10.1097/00006534-200001000-00025] [PMID: 10626983]

[128] Kim HM, Galatz LM, Das R, Havlioglu N, Rothermich SY, Thomopoulos S. The role of transforming growth factor beta isoforms in tendon-to-bone healing. Connect Tissue Res 2011; 52(2): 87-98.
[http://dx.doi.org/10.3109/03008207.2010.483026] [PMID: 20615095]

[129] Tsubone T, Moran SL, Amadio PC, Zhao C, An KN. Expression of growth factors in canine flexor tendon after laceration *in vivo*. Ann Plast Surg 2004; 53(4): 393-7.
[http://dx.doi.org/10.1097/01.sap.0000125501.72773.01] [PMID: 15385778]

[130] Lakemeier S, Reichelt JJ, Patzer T, Fuchs-Winkelmann S, Paletta JR, Schofer MD. The association between retraction of the torn rotator cuff and increasing expression of hypoxia inducible factor 1α and vascular endothelial growth factor expression: an immunohistological study. BMC Musculoskelet Disord 2010; 11: 230.
[http://dx.doi.org/10.1186/1471-2474-11-230] [PMID: 20932296]

[131] Lamplot JD, Angeline M, Angeles J, *et al.* Distinct effects of platelet-rich plasma and BMP13 on rotator cuff tendon injury healing in a rat model. Am J Sports Med 2014; 42(12): 2877-87.
[http://dx.doi.org/10.1177/0363546514547171] [PMID: 25193888]

[132] Handa A, Gotoh M, Hamada K, *et al.* Vascular endothelial growth factor 121 and 165 in the subacromial bursa are involved in shoulder joint contracture in type II diabetics with rotator cuff disease. J Orthop Res 2003; 21(6): 1138-44.
[http://dx.doi.org/10.1016/S0736-0266(03)00102-5] [PMID: 14554230]

[133] Yanagisawa K, Hamada K, Gotoh M, *et al.* Vascular endothelial growth factor (VEGF) expression in the subacromial bursa is increased in patients with impingement syndrome. J Orthop Res 2001; 19(3): 448-55.
[http://dx.doi.org/10.1016/S0736-0266(00)90021-4] [PMID: 11398859]

[134] Chen CH, Chang CH, Wang KC, *et al.* Enhancement of rotator cuff tendon-bone healing with injectable periosteum progenitor cells-BMP-2 hydrogel *in vivo*. Knee Surg Sports Traumatol Arthrosc 2011; 19(9): 1597-607.
[http://dx.doi.org/10.1007/s00167-010-1373-0] [PMID: 21327764]

[135] Seeherman HJ, Archambault JM, Rodeo SA, *et al.* rhBMP-12 accelerates healing of rotator cuff repairs in a sheep model. J Bone Joint Surg Am 2008; 90(10): 2206-19.
[http://dx.doi.org/10.2106/JBJS.G.00742] [PMID: 18829919]

[136] Gulotta LV, Kovacevic D, Packer JD, Ehteshami JR, Rodeo SA. Adenoviral-mediated gene transfer of human bone morphogenetic protein-13 does not improve rotator cuff healing in a rat model. Am J Sports Med 2011; 39(1): 180-7.
[http://dx.doi.org/10.1177/0363546510379339] [PMID: 20956264]

[137] 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.
[PMID: 17974893]

[138] Mazzocca AD, McCarthy MB, Chowaniec D, *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.
[http://dx.doi.org/10.1016/j.arthro.2011.06.029] [PMID: 21978434]

[139] Mazzocca AD, McCarthy MB, Chowaniec DM, Cote MP, Arciero RA, Drissi H. Rapid isolation of human stem cells (connective tissue progenitor cells) from the proximal humerus during arthroscopic rotator cuff surgery. Am J Sports Med 2010; 38(7): 1438-47.
[http://dx.doi.org/10.1177/0363546509360924] [PMID: 20375368]

[140] Valencia Mora M, Ruiz Ibán MA, Díaz Heredia J, Barco Laakso R, Cuéllar R, García Arranz M. Stem cell therapy in the management of shoulder rotator cuff disorders. World J Stem Cells 2015; 7(4): 691-9.
[http://dx.doi.org/10.4252/wjsc.v7.i4.691] [PMID: 26029341]

[141] Pittenger MF, Mackay AM, Beck SC, *et al.* Multilineage potential of adult human mesenchymal stem cells. Science 1999; 284(5411): 143-7.
[http://dx.doi.org/10.1126/science.284.5411.143] [PMID: 10102814]

[142] Paschos NK, Brown WE, Eswaramoorthy R, Hu JC, Athanasiou KA. Advances in tissue engineering through stem cell-based co-culture. J Tissue Eng Regen Med 2015; 9(5): 488-503.
[http://dx.doi.org/10.1002/term.1870] [PMID: 24493315]

[143] Randelli P, Randelli F, Ragone V, *et al.* Regenerative medicine in rotator cuff injuries. Biomed Res Int 2014; 2014: 129515.
[http://dx.doi.org/10.1155/2014/129515]

[144] Beitzel K, McCarthy MB, Cote MP, *et al.* Comparison of mesenchymal stem cells (osteoprogenitors) harvested from proximal humerus and distal femur during arthroscopic surgery. Arthroscopy 2013; 29(2): 301-8.
[http://dx.doi.org/10.1016/j.arthro.2012.08.021] [PMID: 23290182]

[145] Tsai CC, Huang TF, Ma HL, Chiang ER, Hung SC. Isolation of mesenchymal stem cells from shoulder rotator cuff: a potential source for muscle and tendon repair. Cell Transplant 2013; 22(3): 413-22.
[http://dx.doi.org/10.3727/096368912X656090] [PMID: 23006509]

[146] Randelli P, Conforti E, Piccoli M, *et al.* Isolation and characterization of 2 new human rotator cuff and long head of biceps tendon cells

possessing stem cell-like self-renewal and multipotential differentiation capacity. Am J Sports Med 2013; 41(7): 1653-64.
[http://dx.doi.org/10.1177/0363546512473572] [PMID: 23393078]

[147] Izadpanah R, Trygg C, Patel B, *et al.* Biologic properties of mesenchymal stem cells derived from bone marrow and adipose tissue. J Cell Biochem 2006; 99(5): 1285-97.
[http://dx.doi.org/10.1002/jcb.20904] [PMID: 16795045]

[148] 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.
[http://dx.doi.org/10.1177/0363546512473269] [PMID: 23371475]

[149] Song N, Armstrong AD, Li F, Ouyang H, Niyibizi C. Multipotent mesenchymal stem cells from human subacromial bursa: potential for cell based tendon tissue engineering. Tissue Eng Part A 2014; 20(1-2): 239-49.
[http://dx.doi.org/10.1089/ten.tea.2013.0197] [PMID: 23865619]

[150] Gulotta LV, Kovacevic D, Montgomery S, Ehteshami JR, Packer JD, Rodeo SA. Stem cells genetically modified with the developmental gene MT1-MMP improve regeneration of the supraspinatus tendon-to-bone insertion site. Am J Sports Med 2010; 38(7): 1429-37.
[http://dx.doi.org/10.1177/0363546510361235] [PMID: 20400753]

[151] Gulotta LV, Kovacevic D, Packer JD, Deng XH, Rodeo SA. Bone marrow-derived mesenchymal stem cells transduced with scleraxis improve rotator cuff healing in a rat model. Am J Sports Med 2011; 39(6): 1282-9.
[http://dx.doi.org/10.1177/0363546510395485] [PMID: 21335341]

[152] Kida Y, Morihara T, Matsuda K, *et al.* Bone marrow-derived cells from the footprint infiltrate into the repaired rotator cuff. J Shoulder Elbow Surg 2013; 22(2): 197-205.
[http://dx.doi.org/10.1016/j.jse.2012.02.007] [PMID: 22543003]

[153] Yokoya S, Mochizuki Y, Natsu K, Omae H, Nagata Y, Ochi M. Rotator cuff regeneration using a bioabsorbable material with bone marrow-derived mesenchymal stem cells in a rabbit model. Am J Sports Med 2012; 40(6): 1259-68.
[http://dx.doi.org/10.1177/0363546512442343] [PMID: 22491821]

[154] Kim YS, Lee HJ, Ok JH, Park JS, Kim DW. Survivorship of implanted bone marrow-derived mesenchymal stem cells in acute rotator cuff tear. J Shoulder Elbow Surg 2013; 22(8): 1037-45.
[http://dx.doi.org/10.1016/j.jse.2012.11.005] [PMID: 23246275]

[155] Oh JH, Chung SW, Kim SH, Chung JY, Kim JY. 2013 Neer Award: Effect of the adipose-derived stem cell for the improvement of fatty degeneration and rotator cuff healing in rabbit model. J Shoulder Elbow Surg 2014; 23(4): 445-55.
[http://dx.doi.org/10.1016/j.jse.2013.07.054] [PMID: 24129058]

[156] Pelinkovic D, Lee JY, Engelhardt M, *et al.* Muscle cell-mediated gene delivery to the rotator cuff. Tissue Eng 2003; 9(1): 143-51.
[http://dx.doi.org/10.1089/107632703762687627] [PMID: 12625963]

[157] Shen W, Chen J, Yin Z, *et al.* Allogenous tendon stem/progenitor cells in silk scaffold for functional shoulder repair. Cell Transplant 2012; 21(5): 943-58.
[http://dx.doi.org/10.3727/096368911X627453] [PMID: 22405331]

[158] Ellera Gomes JL, da Silva RC, Silla LM, Abreu MR, Pellanda R. Conventional rotator cuff repair complemented by the aid of mononuclear autologous stem cells. Knee Surg Sports Traumatol Arthrosc 2012; 20(2): 373-7.
[http://dx.doi.org/10.1007/s00167-011-1607-9] [PMID: 21773831]

[159] Hernigou P, Flouzat Lachaniette CH, Delambre J, *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.
[http://dx.doi.org/10.1007/s00264-014-2391-1] [PMID: 24913770]

[160] Protzman NM, Stopyra GA, Hoffman JK. Biologically enhanced healing of the human rotator cuff: 8-month postoperative histological evaluation. Orthopedics 2013; 36(1): 38-41.
[http://dx.doi.org/10.3928/01477447-20121217-06] [PMID: 23276334]

[161] Gordon NM, Maxson S, Hoffman JK. Biologically enhanced healing of the rotator cuff. Orthopedics 2012; 35(6): 498-504.
[http://dx.doi.org/10.3928/01477447-20120525-06] [PMID: 22691639]

[162] Lo IK, Marchuk LL, Hollinshead R, Hart DA, Frank CB. Matrix metalloproteinase and tissue inhibitor of matrix metalloproteinase mRNA levels are specifically altered in torn rotator cuff tendons. Am J Sports Med 2004; 32(5): 1223-9.
[http://dx.doi.org/10.1177/0363546503262200] [PMID: 15262646]

[163] Choi HR, Kondo S, Hirose K, Ishiguro N, Hasegawa Y, Iwata H. Expression and enzymatic activity of MMP-2 during healing process of the acute supraspinatus tendon tear in rabbits. J Orthop Res 2002; 20(5): 927-33.
[http://dx.doi.org/10.1016/S0736-0266(02)00016-5] [PMID: 12382955]

[164] Yoshihara Y, Hamada K, Nakajima T, Fujikawa K, Fukuda H. Biochemical markers in the synovial fluid of glenohumeral joints from patients with rotator cuff tear. J Orthop Res 2001; 19(4): 573-9.
[http://dx.doi.org/10.1016/S0736-0266(00)00063-2] [PMID: 11518264]

[165] Garofalo R, Cesari E, Vinci E, Castagna A. Role of metalloproteinases in rotator cuff tear. Sports Med Arthrosc Rev 2011; 19(3): 207-12.
[http://dx.doi.org/10.1097/JSA.0b013e318227b07b] [PMID: 21822103]

[166] Del Buono A, Oliva F, Longo UG, *et al.* Metalloproteases and rotator cuff disease. J Shoulder Elbow Surg 2012; 21(2): 200-8.

[http://dx.doi.org/10.1016/j.jse.2011.10.020] [PMID: 22244063]

[167] Castagna A, Cesari E, Garofalo R, *et al.* Matrix metalloproteases and their inhibitors are altered in torn rotator cuff tendons, but also in the macroscopically and histologically intact portion of those tendons. Muscles Ligaments Tendons J 2013; 3(3): 132-8.
[PMID: 24367772]

[168] Bedi A, Fox AJ, Kovacevic D, Deng XH, Warren RF, Rodeo SA. Doxycycline-mediated inhibition of matrix metalloproteinases improves healing after rotator cuff repair. Am J Sports Med 2010; 38(2): 308-17.
[http://dx.doi.org/10.1177/0363546509347366] [PMID: 19826139]

[169] Brown BN, Valentin JE, Stewart-Akers AM, McCabe GP, Badylak SF. Macrophage phenotype and remodeling outcomes in response to biologic scaffolds with and without a cellular component. Biomaterials 2009; 30(8): 1482-91.
[http://dx.doi.org/10.1016/j.biomaterials.2008.11.040] [PMID: 19121538]

[170] Hodde JP, Ernst DM, Hiles MC. An investigation of the long-term bioactivity of endogenous growth factor in OASIS Wound Matrix. J Wound Care 2005; 14(1): 23-5.
[http://dx.doi.org/10.12968/jowc.2005.14.1.26721] [PMID: 15656461]

[171] Hodde JP, Record RD, Liang HA, Badylak SF. Vascular endothelial growth factor in porcine-derived extracellular matrix. Endothelium 2001; 8(1): 11-24.
[http://dx.doi.org/10.3109/10623320109063154] [PMID: 11409848]

[172] Derwin KA, Badylak SF, Steinmann SP, Iannotti JP. Extracellular matrix scaffold devices for rotator cuff repair. J Shoulder Elbow Surg 2010; 19(3): 467-76.
[http://dx.doi.org/10.1016/j.jse.2009.10.020] [PMID: 20189415]

[173] Ricchetti ET, Aurora A, Iannotti JP, Derwin KA. Scaffold devices for rotator cuff repair. J Shoulder Elbow Surg 2012; 21(2): 251-65.
[http://dx.doi.org/10.1016/j.jse.2011.10.003] [PMID: 22244069]

[174] Baumgarten KM, Oliver HA, Foley J, *et al.* Human growth hormone may be detrimental when used to accelerate recovery from acute tendon-bone interface injuries. J Bone Joint Surg Am 2013; 95(9): 783-9.
[http://dx.doi.org/10.2106/JBJS.L.00222] [PMID: 23636184]

[175] Thomopoulos S, Hattersley G, Rosen V, *et al.* The localized expression of extracellular matrix components in healing tendon insertion sites: an *in situ* hybridization study. J Orthop Res 2002; 20(3): 454-63.
[http://dx.doi.org/10.1016/S0736-0266(01)00144-9] [PMID: 12038618]