The Role of Platelet Rich Plasma (PRP) and Other Biologics for Rotator Cuff Repair

Joshua A. Greenspoon¹, Samuel G. Moulton¹, Peter J. Millett¹,²*, and Maximilian Petri¹,²

¹Steadman Philippon Research Institute, 181 West Meadow Drive, Suite 1000 Vail, CO, 81657, USA
²The Steadman Clinic, 181 West Meadow Drive Vail, CO, 81657, USA

Received: August 02, 2015 | Revised: August 07, 2015 | Accepted: February 1, 2016

Abstract:

Background:

Surgical treatment of rotator cuff tears has consistently demonstrated good clinical and functional outcomes. However, in some cases, the rotator cuff fails to heal. While improvements in rotator cuff constructs and biomechanics have been made, the role of biologics to aid healing is currently being investigated.

Methods:

A selective literature search was performed and personal surgical experiences are reported.

Results:

Biologic augmentation of rotator cuff repairs can for example be performed with platelet-rich plasma (PRP) and mesenchymal stem cells (MSCs). Clinical results on PRP application have been controversial. Application of MSCs has shown promise in animal studies, but clinical data on its effectiveness is presently lacking. The role of Matrix Metalloproteinase (MMP) inhibitors is another interesting field for potential targeted drug therapy after rotator cuff repair.

Conclusions:

Large randomized clinical studies need to confirm the benefit of these approaches, in order to eventually lower retear rates and improve clinical outcomes after rotator cuff repair.

Keywords: Biologics, Platelet rich plasma, Regenerative medicine, Rotator cuff, Shoulder, Stem cells.

INTRODUCTION

The goal of rotator cuff repair is to restore function, improve pain, and to achieve healing of the involved tendons. Significant improvements in the biomechanics of rotator cuff repair constructs have been made over the past decade [1 - 3]. However, reported retear rates following rotator cuff repair have remained high [4 - 6]. Therefore attention has turned to ways in which the healing environment can be enhanced to promote healing of the rotator cuff tendons back to the bone. Specifically, biologically active materials have been designed to enhance the strength and quality of the repaired tissue at the tendon footprint. Many biologic factors contribute to the coordination and implementation of the healing response. In an attempt to augment healing after surgery, many investigators have studied how to enhance physiologic healing. These include addition of growth factors and cells to the repair site as well as the use of suture materials and different surgical repair techniques. The purpose of this paper is to highlight the role of platelet rich

* Address Correspondence to this author at the Steadman Philippon Research Institute, 181 West Meadow Drive, Suite 1000 Vail, CO, 81657, USA; E-mail: drmillett@thesteadmanclinic.com
plasma (PRP) and other biologic agents used to enhance healing in rotator cuff repair.

OVERVIEW OF TENDON HEALING

When a tendon is injured, the body employs a complex healing response involving many signaling molecules. Generally, the healing process is thought to occur in three overlapping stages. The first stage (or "inflammatory phase") is an acute response lasting several days in which an inflammatory response results in infiltration of the wound site with red blood cells, leukocytes, and platelets [7]. The platelets contain important signaling molecules that coordinate the repair process. A fibrin clot is formed allowing for macrophages to remove necrotic waste [7]. Tenocytes are recruited and proliferate. The second stage (or "proliferative phase") begins approximately two days after injury [7]. Macrophages assume a reparative role and release growth factors as well as signaling molecules to recruit additional cells. Tenocytes start synthesizing a temporary matrix composed primarily of type III collagen [7]. The third or "remodeling" phase of healing begins 1-2 months after injury in which the type III collagen is replaced by biomechanically superior type I collagen.

PLATELET RICH PLASMA (PRP)

Platelet rich plasma (PRP) is a centrifuged blood product that contains a supraphysiologic amount of platelets. These platelets release biologic factors including basic fibroblast growth factor (FGF2), vascular endothelial growth factor (VEGF), and transforming growth factor β (TGF β) which have been shown to improve proliferation and collagen secretion of tenocytes in vitro [8 - 11]. In addition to promoting tendon cell growth, PRP has been shown to decrease oxidative stress that could lead to cell apoptosis [12].

Several studies have investigated the clinical results PRP has on rotator cuff healing [13 - 22]. Malavolta et al. recently published the results of their randomized controlled trial investigating the structural and functional outcomes of rotator cuff repairs with or without PRP at the time of surgery [17]. The two groups of 27 patients had complete full thickness tears of the supraspinatus and underwent single row repairs with or without the use of PRP. Both groups had significant improvement in functional scores at 2 years of follow-up as measured by the Constant and University of California at Los Angeles (UCLA) scores [17]. Overall, there were no differences in outcomes at 24 months between the two groups. In addition, the two groups had comparable retear rates as determined by magnetic resonance imaging (MRI) [17].

Wang et al. conducted a well-designed randomized controlled study investigating if PRP injections at 7 and 14 days postoperatively improved healing and early functional recoveries [20]. Sixty patients underwent arthroscopic double-row surgeries, half of which received postoperative PRP injections. Healing was assessed at 16 weeks postoperatively using MRI [20]. The authors concluded that PRP treatment did not improve early functional recovery, range of motion, strength, or pain levels. Furthermore, there was no statistically significant difference in structural integrity of the repair between the two groups [20]. However, there were 2 full thickness retears in the control group and 0 in the PRP group. This finding is consistent with previous reports, such as that of Castricini et al. who reported a higher rerupture rate in their control group of 10.5% vs 2.5% in the PRP group [14]. Their patient cohort consisted of 88 patients randomly assigned to two groups and completed a Constant score and had an MRI an average of 20 months postoperatively.

Charousset et al. conducted a case-control study with the intention of determining functional and structural differences between patients with double row rotator cuff repairs with or without PRP injections [23]. There were no differences in rotator cuff healing as assessed by MRI between the two groups. The retear rate was 35.5% for the PRP group and 40% for the control group [23]. However the size of the recurrent tears was smaller in the group of patients who received PRP [23]. Similar to the studies mentioned above, there were no functional differences between the two groups at a minimum of two years postoperatively.

A randomized controlled trial conducted by Jo et al. showed improvement in structural outcomes in patients who underwent arthroscopic rotator cuff repair of large to massive tears and received PRP [16]. There was a significantly lower retear rate in patients who received PRP (3.0%) compared to those who did not (20.0%) [16]. Patients who received PRP also had significantly larger cross sectional areas of the supraspinatus, leading the authors to conclude that PRP use increases the quality of the tendon healing postoperatively [16]. Importantly, PRP did not increase the speed of healing, and functional outcomes between the two groups were equivalent [16].

In a separate randomized controlled study, Randelli et al. found less postoperative pain and accelerated healing rates in patients with non- massive rotator cuff tears when PRP was used [18]. A total of 53 patients were included. The
The Role of Platelet Rich Plasma (PRP) in the Healing of Rotator Cuff Tears

UCLA, SST, Constant scores, and strength in external rotation were significantly higher in the PRP group at 3 months postoperatively, however, these differences were not evident at 6, 12, or 24 months postoperatively [18].

Given the conflicting results and varying protocols of the studies investigating PRP in the setting of rotator cuff repair, several authors have conducted meta-analyses of these studies in order to further assess the data [24, 25]. Warth et al. analyzed 11 level 1 or level 2 studies [25]. The results of the meta-analysis indicated that there were no global differences in clinical outcomes between patients who received PRP and those that did not [25]. Meta-regression did indicate that the overall gain in the Constant score was increased when PRP was placed at the tendon bone interface rather than over the surface of the repaired tendon [25]. Subgroup analysis revealed significantly lower retear rates with PRP application in patients who underwent double-row repairs for large (> 3 cm) rotator cuff tears [25]. This finding is of particular interest, as retear rates in large and massive rotator cuff tears are much higher than in smaller tears, making large and massive tears the main target for adjuncts to improve healing.

Vavken et al. conducted a meta-analysis and cost-effectiveness analysis on the use of PRP based on 13 published studies [24]. Different to the findings of Warth et al. the authors found PRP to be effective in reducing retear rates in the arthroscopic repair of small and medium sized rotator cuff tears, however there was no evidence that retear rates decreased for large and massive tears [24]. With the current cost of PRP, the cost-effectiveness analysis indicated that the use of PRP is currently not cost-effective [24]. The reductions in retear rates for small and medium sized rotator cuff tears is consistent with a trend noted in a systematic review by Chahal et al. [26]. While the impact of PRP injections on retear rates differed based on tear size in the two meta-analyses, overall the two reviews suggest PRP may play a role in the healing of rotator cuff repairs.

Given the inconsistent clinical results, the use of PRP to enhance healing of the rotator cuff following surgery remains an area of debate. Additional basic science research is needed to enhance our understanding of the tendon healing process and future randomized clinical studies with sufficient sample sizes are needed to determine the optimal timing, preparation, and concentration of PRP products to enhance physiologic healing.

MATRIX METALLOPROTEINASE (MMP) INHIBITORS

Matrix metalloproteinases (MMPs) are zinc-dependent proteases that maintain and model the extracellular matrix [27]. While numerous MMPs exist, generally their role in remodeling extracellular matrix inhibits tendon healing following rotator cuff repair. The tetracycline family of antibiotics has properties independent of their antimicrobial activity that allows them to inhibit MMPs and therefore reduce degradation and remodeling after rotator cuff repair [27]. Bedi and colleagues used a rat model to analyze the effects of oral doxycycline taken after rotator cuff repair [27]. They found that the perioperative use of doxycycline influences early healing after rotator cuff repair, resulting in greater amounts of fibrocartilage as well as improved collagen organization. When the repair was tested biomechanically, the group treated with doxycycline had a significantly greater load to failure at 2 weeks compared to controls [27].

In contrast, fluoroquinolone antibiotics have been argued to potentially favour tendinopathy and tendon ruptures. Accordingly, Fox et al. recently reported that fluoroquinolone treatment negatively influenced tendon healing in rats who underwent rotator cuff repair [28].

Of particular relevance in orthopaedic surgery, the use of the non-steroidal anti-inflammatory drug (NSAID) diclofenac was shown to significantly influence levels of MMP-2, MMP-3 and MMP-13 after rotator cuff repair in a rat model, eventually resulting in decreased biomechanical strength of the repair [29]. Cohen et al. demonstrated inferior healing and lower rotator cuff repair loads to failure in rats receiving celecoxib and indomethacin compared to controls [30]. In addition, the collagen was more organized in the control groups. This raises the question whether the use of NSAIDs after rotator cuff repair should be limited to avoid disturbance of the healing process.

Gotot et al. found increased levels of MMP-3 and tissue inhibitor of MMP (TIMP)-1 in patients with rotator cuff tears who sustained re-tears after repair compared to those who did not [31]. These results suggest that up-regulation of TIMP-1 and MMP-3 is associated with postoperative tendon retear. This offers a potential research approach for targeted drug therapy after rotator cuff repair [31].

STEM CELL THERAPY

Mesenchymal stem cells (MSCs) derived from various origins have been investigated in animal studies to determine if their differentiation potential can be used to enhance healing of the rotator cuff tendon. Gulotta et al. investigated...
bone marrow derived MSCs in a rat model [32]. The investigators found evidence that the MSCs were present and metabolically active, however, the addition of MSCs to the healing rotator cuff insertion site did not improve the structure, composition, or strength of the healing tendon [32]. Using a rat model, Kida et al. simulated rotator cuff tears and repairs [33]. In one group, they drilled additional holes into the greater tuberosity to promote mesenchymal stem cell migration [20]. The authors found that the rats with the additional holes had more MSCs than the other group and there was also a higher ultimate force-to-failure of the repair [33]. Oh et al. used a rabbit model to investigate the effects of administration of adipose derived stem cells had on tendon healing and fatty infiltration [26]. They concluded that adipose derived stem cells may be able to improve muscle function, tendon healing, and decrease fatty infiltration after rotator cuff repair [34].

Clinical studies investigating MSCs are currently sparse. Beitzel et al. demonstrated that MSCs can be harvested in a reliable, consistent fashion from either the proximal humerus or distal femur [35]. Hernigou et al. collected bone marrow aspiration samples from the greater tuberosity in 125 patients with rotator cuff tears, and compared them to the samples of 75 patients with a healthy rotator cuff regarding the amount of MSCs [36]. Patients with rotator cuff tears showed a significant reduction in MSC content at the tendon-bone interface compared to the control group. Lower counts of MSCs were statistically correlated to patients age, delayed onset of symptoms and surgery, number of involved tendons, and fatty infiltration stage [36]. This study emphasizes the potential benefit of biologic augmentation in rotator cuff repair.

Ellera Gomes et al. published a study on 14 consecutive patients who underwent mini-open rotator cuff repair along with injection of autologous bone marrow mononuclear cells [37]. Magnetic resonance imaging analysis 12 months postoperatively demonstrated tendon integrity in all cases. Additional studies are needed to understand how to best utilize stem cells to promote tendon healing and quality.

CONCLUSION

Basic science studies investigating biologic factors to enhance healing of the rotator cuff show promise. However, clinical data is sparse, inconsistent and controversial. Further investigations are required to determine the best biological agents, uses, concentrations and routes of application. Presently we use PRP to augment healing in biologically challenged cases such as in revision repairs, immaissive tears with poor quality tissue, and in biologically challenged hosts such as smokers and diabetics. We avoid the use of NSAIDS for 6 weeks post repair in all cases.

CONFLICT OF INTEREST

The authors report the following potential conflict of interest or source of funding: JAG, SJM, PJM, MP receive support from Steadman Philippon Research Institute. Corporate sponsorship for Steadman Philippon Research Institute is received from Ossur, Smith & Nephew Endoscopy, Siemens Medical Solutions, and Arthrex. P.J.M. also receives support from Arthrex, Myos, GameReady, and VuMedi.MP received support from Arthrex Inc.

ACKNOWLEDGEMENTS

Declared none

REFERENCES

[1] Millett PJ, Mazzocca A, Guanche CA. Mattress double anchor footprint repair: a novel, arthroscopic rotator cuff repair technique. Arthroscopy 2004; 20(8): 875-9. [http://dx.doi.org/10.1016/S0749-8063(04)00080-4] [PMID: 15483553]

[2] Vaishnav S, Millett PJ. Arthroscopic rotator cuff repair: scientific rationale, surgical technique, and early clinical and functional results of a knotless self-reinforcing double-row rotator cuff repair system. J Shoulder Elbow Surg 2010; 19(2 Suppl): 83-90. [http://dx.doi.org/10.1016/j.jse.2009.12.012] [PMID: 20188272]

[3] van der Meijden OA, Wijdicks CA, Gaskill TR, Jansson KS, Millett PJ. Biomechanical analysis of two-tendon posterosuperior rotator cuff tear repairs: extended linked repairs and augmented repairs. Arthroscopy 2013; 29(1): 37-45. [http://dx.doi.org/10.1016/j.arthro.2012.07.012] [PMID: 23276412]

[4] Boyer P, Bouthors C, Delcourt T, et al. Arthroscopic double-row cuff repair with suture-bridging: a structural and functional comparison of two techniques. Knee Surg Sports Traumatol Arthrosc 2015; 23(2): 478-86. [http://dx.doi.org/10.1007/s00167-013-2401-7] [PMID: 23404511]

[5] Millett PJ, Warth RJ, Dornan GJ, Lee JT, Spiegl UJ. Clinical and structural outcomes after arthroscopic single-row versus double-row rotator cuff repair: a systematic review and meta-analysis of level I randomized clinical trials. J Shoulder Elbow Surg 2014; 23(4): 586-97. [http://dx.doi.org/10.1016/j.jse.2013.10.006] [PMID: 24411671]
[6] Rhee YG, Cho NS, Parke CS. Arthroscopic rotator cuff repair using modified Mason-Allen medial row stitch: knotless versus knot-tying suture bridge technique. Am J Sports Med 2012; 40(11): 2440-7. [PMID: 23002202]

[7] Voleti PB, Buckley MR, Soslowsky LJ. Tendon healing: repair and regeneration. Annu Rev Biomed Eng 2012; 14: 47-71. [PMID: 22809137]

[8] Hee CK, Dines IS, 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. [PMID: 21555508]

[9] Ide J, Kikukawa K, Hirose J, Ivama 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. [PMID: 19010104]

[10] Ide J, Kikukawa K, Hirose J, et al. The effect of a local application of fibroblast growth factor-2 on tendon-to-bone remodeling in rats with acute injury and repair of the supraspinatus tendon. J Shoulder Elbow Surg 2009; 18(3): 391-8. [PMID: 19393930]

[11] 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. [PMID: 21246611]

[12] Lane JG, Healey RM, Chase DC, Amiel D. Use of platelet-rich plasma to enhance tendon function and cellularity. Am J Orthop 2013; 42(5): 209-14. [PMID: 23710476]

[13] 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. [PMID: 22016459]

[14] 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. [PMID: 21160018]

[15] Hak A, Rajaratnam K, Ayeni OR, et al. A double-blinded placebo randomized controlled trial evaluating short term efficacy of platelet rich plasma in reducing postoperative pain after arthroscopic rotator cuff repair: a pilot study. Sports Health 2015; 7(1): 58-66. [PMID: 25553214]

[16] 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 2015; 43: 2102-10. [PMID: 26015443]

[17] Malavolta EA, Gracitielli 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. [PMID: 25086065]

[18] 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. [PMID: 21570659]

[19] 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. [PMID: 22809137]

[20] 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. [PMID: 25908355]

[21] Weber SC, Kauffman JI, Parise C, Weber SJ, Katz SD. Platelet-rich fibrin matrix in the management of arthroscopic repair of the rotator cuff: a prospective, randomized, double-blinded study. Am J Sports Med 2013; 41(2): 263-70. [PMID: 23204506]

[22] Zumstein MA, Rumian A, Lesbats V, Schaefer M, Boileau P. Increased vascularization during early healing after biological augmentation in repair of chronic rotator cuff tear using autologous leukocyte- and platelet-rich fibrin (L-PRF): a prospective randomized controlled pilot trial. J Shoulder Elbow Surg 2014; 23(1): 3-12. [PMID: 24331121]

[23] Charousset C, Zaoui A, Bellache 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. [PMID: 24680303]

[24] Vavken P, Sadoghi P, Palmer M, et al. Platelet-rich plasma reduces retear rates after arthroscopic repair of small and medium-sized rotator cuff tears but is not cost-effective. Am J Sports Med 2015; 43(12): 3071-6. [PMID: 25767267]
[25] Warth RJ, Dorman GJ, James EW, Horan MP, Millett PJ. Clinical and structural outcomes after arthroscopic repair of full-thickness rotator cuff tears with and without platelet-rich product supplementation: a meta-analysis and meta-regression. Arthroscopy 2015; 31(2): 306-20. [http://dx.doi.org/10.1016/j.arthro.2014.09.007] [PMID: 25450417]

[26] Chahal J, Van Thiell 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]

[27] Bedi A, Fox AJ, Kovacevic D, Deng XH, Warrin 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]

[28] Fox AJ, Schär MO, Wanivenhaus F, et al. Fluoroquinolones impair tendon healing in a rat rotator cuff repair model: a preliminary study. Am J Sports Med 2014; 42(12): 2851-9. [http://dx.doi.org/10.1177/0363546514545858] [PMID: 25143490]

[29] Cabuk H, Avei A, Darmaz H, Cabuk FK, Ertum F, Muhittin Şener I. The effect of diclofenac on matrix metalloproteinase levels in the rotator cuff. Arch Orthop Trauma Surg 2014; 134(12): 1739-44. [http://dx.doi.org/10.1007/s00402-014-2099-0] [PMID: 25362529]

[30] Cohen DB, Kawamura S, Ehteshami JR, Rodeo SA. Indomethacin and celecoxib impair rotator cuff tendon-to-bone healing. Am J Sports Med 2006; 34(3): 362-9. [http://dx.doi.org/10.1177/0363546505280428] [PMID: 16210573]

[31] Goto M, Mitsui Y, Shibata H, et al. Increased matrix metalloprotease-3 gene expression in ruptured rotator cuff tendons is associated with postoperative tendon retear. Knee Surg Sports Traumatol Arthrosc 2013; 21(8): 1807-12. [http://dx.doi.org/10.1007/s00167-012-2209-a] [PMID: 23000921]

[32] 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/10.1016/j.ajsm.2009.02.007] [PMID: 19684297]

[33] 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]

[34] 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]

[35] 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]

[36] Hernigou P, Merouse G, Duffiet P, Chevalier N, Rouard H. Reduced levels of mesenchymal stem cells at the tendon-bone interface tuberosity in patients with symptomatic rotator cuff tear. Int Orthop 2015; 39(6): 1219-25. [http://dx.doi.org/10.1007/s00264-015-2724-8] [PMID: 25757411]

[37] Ellera GJL, 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]