The role of adipose derived stem cells in the treatment of rotator cuff tears: from basic science to clinical application

Fabrizio Mocini, Andrea Stefano Monteleone, Piero Piazza, Valentina Cardona, Valeria Vismara, Piermarco Messinese, Vincenzo Campana, Giuseppe Sircana, Giulio Maccauro, Maristella Francesca Saccomanno

Orthopaedic Institute, Fondazione Policlinico Universitario A. Gemelli, IRCSS, Rome, Italy

Abstract

Over the last decade, regenerative medicine has become increasingly popular throughout the scientific community. The poor healing capacity at the tendon-bone interface makes the rotator cuff an appealing target for biologic agents. Adipose derived stem cells are mesenchymal cells with the capacity for self-renewal and multipotential differentiation. They have been recently proposed, both in isolation and as adjuvants to existing surgical therapies, for the treatment of rotator cuff tears. Several studies have been carried out in this research field, starting from the biological characteristics of adipose derived stem cells, their preparation and culture, up to the application in the experimental field on animal models and on humans. The purpose of this study was to provide a state of the art about the current basic science and clinical literature for the effectiveness of adipose derived stem cells in the treatment of rotator cuff tears.

Introduction

Rotator cuff tears (RCTs) are a common condition that causes shoulder pain and dysfunction in over 20% of the general adult population, with a progressively higher incidence as age increases.[1-3]

The treatment for RCTs can be conservative (rest, physical therapy, non-steroidal anti-inflammatory drugs and corticosteroid injection) or surgical (arthroscopic or open repair), depending on the type of lesion (partial- or full-thickness, size, retraction) and patient characteristics (age, comorbidity, functional request). Conservative treatment can reduce symptoms but cannot restore the structure of rotator cuff neither avoiding the progress of the pathology.[4,5] Moreover, a considerable number of patients (25%) complain of persistent symptoms after 5 years of conservative treatment.[6] Regarding the surgical treatment, although functional outcomes do not always correlate with the structural integrity after repair,[7] the re-rupture rate after surgical repair is estimated between 11% and 94%.[8,9]

The poor healing response of the rotator cuff healing is most likely multifactorial,[10-12] and may include an insufficient number of mesenchymal stem cells at the healing tendon-bone interface. These cells contribute to homoeostasis, remodeling, and repair through paracrine mechanism. [13] The weak healing capacity makes the rotator cuff an appealing target for biologic agents. In the last decade, there has been a rapid growth in the number of available agents, used both for nonoperative therapeutic option through injections and as adjuvant to existing surgical repair techniques.

Platelet rich plasma (PRP) has been the first biologic agent to be widely utilized. It is relatively easy to harvest but the main disadvantage is the variability of composition between patients. Although *in vitro* studies support a potential role in the use of PRP in both nonoperative and operative treatment of RCTs, clinical data are still controversial. Reduction of postoperative pain has been found at short-term follow-up, yet not in the long-term follow-up.[14,15] Bone marrow derived stem cells (BMCs) concentrate is another commonly used biologic adjuvant. Although it contains more growth factors and 3 times more nucleated cells than PRP,[8,9] its true clinical efficacy for the treatment of RCTs is still controversial and scarce.

In more recent years adipose-derived stem cells (ADSCs) concentrate has been proposed. ADSCs differentiated from mesenchymal stem cells and they have been discovered in the early 2000s showing their great ability of multilineage proliferation and self-renewal. [9] Particularly the ADSCs, which are able to differentiate into myocytes, tenocytes and into other mesenchymal stem cells, increase angiogenesis, matrix synthesis and alter the inflammatory markers which alongside the effectiveness of pain reduction and tissue regeneration has increased the interest of their clinical use in many physicians over the years. This capacity of a multipotent differentiation potential has been demonstrated both *in vitro* and *in vivo*. [16,17]

Therefore, the purpose of this study was to provide a state of the art about the current basic science and clinical literature for the effectiveness of ADSCs in the treatment of RCTs.

Correspondence: Fabrizio Mocini, Orthopaedic Institute, Fondazione Policlinico Universitario A. Gemelli, IRCSS, Rome, Italy.
E-mail: fabriziomocini90@gmail.com

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ADSCs: harvesting, preparation and cellular characteristics

The most widely used ADSCs isolation protocol was described by Zuk *et al*.[18] This isolation consists in 8 steps: obtaining adipose tissue by liposuction in subcutaneous space, washing of the raw lipoaspirate, enzymatic digestion, centrifugation, lysis of contaminating red blood cells, filtration process, incubation, washing to remove residual red blood cells. The final product obtained is a processed lipoaspirate (PLA), which must be stored at 37°C/5% CO2.[18] From this protocol several studies have tested and implemented different methods of isolation, relying, in particular, on the use of different enzymes or the use of mechanically process.[19-23] In the collagenase method the adipose tissue is washed extensively with phosphate buffered saline (PBS) and digested with 1 mg collagenase type I. [19] Red blood cell lysis buffer solution (LBS) method is based on simultaneous mechanical shaking incubation with red blood cell lysis solution.[20] In trypsin method the ADSCs are isolated by simultaneous shaking and trypsin enzymatic at different con-

centration each 10 minutes. Also enzymatic digestion methods have shown the possibility to affect cell viability, multipotency, senescence and cell surface antigen expression.[21] Centrifugation method consists in the no-use of enzymatic digestion but only using centrifugation at various speed for 15 minutes. The advantage of the mechanical method is legislative, as for the current European legislation the ADSCs must be mechanically isolated, while methods that provide for enzymatic digestion involve the destruction of the contact between the cells thus constituting a manipulation.[22] The disadvantages, on the other hand, consist in the need to use a large quantity of lipoaspirate and in the low viability of the resulting isolated ADSCs, thus making the non-enzymatic methods less efficient than the enzymatic ones.[23] For injection a 22 gauge needle can be used with ultrasonic guidance and under sterile conditions as it's described by Freitag and Wickham in their case report.[24] One milliliter of human subcutaneous adipose tissue contains on average about 100,000 to 500,000 nucleated cells.[25] The majority of ADSCs express the stromal markers CD9, CD10, CD29, CD44, CD73, CD90, and CD166 with the exception of HLA-AB.[26,27] Moreover, ADSCs are positive for pericytic markers such as 3G5 and CD146.[28,29] In addition, ADSCs are able to secrete a range of growth factors and of both hematopoietic and proinflammatory cytokines, having significant paracrine effects.[16,30-34] Concerning the hematopoietic cytokines, Kilroy *et al*.[30] have shown the secretion of granulocyte/monocyte, granulocyte, interleukin 7 and macrophage colony stimulating factors; while for the proinflammatory ones they have proved the release of interleukins 6, 8, 11 and tumor necrosis factor alpha.[30] Therefore, the expression of several stromal markers, the secretion of growth factors and of both hematopoietic and proinflammatory cytokines are important factors for the improvement of tissue healing and recovery. Schäffler *et al*.[35] in 2007 stated in a review that in the treatment of joint pathologies both ADSCs and BMCs could be used because of their equal potential to differentiate into bone, muscle or tendon cells. However, the fact that subcutaneous adipose tissue is a relatively accessible reservoir for adult stem cell harvest and that ADSCs are less influenced by age or morbidity of patients in contrast of BMCs, thus working in favor of the clinical use of ADSCs.[36] Moreover, bone marrow aspirate concentrate has shown to have less stem cells per unit volume than ADSCs.[37] In addition, ADSCs do not provoke a strong lymphocytic reaction but they instead release immunosuppressive factors that enable the allogeneic and autologous ADSCs to engraft successfully for musculoskeletal tissue regeneration purposes.[25]

Basic science evidence on animal models

Chronic RCTs have been studied by Oh *et al*.[38] in 2014. They conducted a study in order to verify the effects of ADSCs on tendon healing in a rabbit model. The insertions of the subscapularis tendon were bilaterally cut in 32 rabbits. After 6 weeks, secondary procedures were performed: the animals were divided into 5 groups: the ADSCs+repair, saline+repair, ADSCs-only, saline-only and control group. Six weeks later, the ADSCs+repair group exhibited a larger compound muscle action potential area than other groups on electromyographic evaluation, almost at the level of the control group. Histologically, the ADSCs+repair group showed a lower fat proportion than the saline+repair group and the ASC-only was lower than that of the saline-only.

Mora *et al*.[39] in 2014 performed a study on 50 rats that underwent detachment and repair of the supraspinatus tendon. Animals were randomized in two groups to receive either a collagen carrier alone or the carrier addiction with ADSCs. Although the application of ADSCs did not improve the biomechanical properties of the tendon-to-bone healing at 2 and 4 weeks, the ADSCs group showed less inflammation, which may lead to a more elastic repair and less scarred healing.

Lipner *et al*.[40] in 2015 examined the effect of an aligned nanofibrous poly lactic co-glycolic acid scaffold seeded with ADSCs and implanted at the repair site of rotator cuff in 64 rats. The healing response was examined in four groups (suture only, acellular scaffold, cellular scaffold, and cellular+BMP2 scaffold) using histologic, bone morphology, and biomechanics outcomes at 14, 28, and 56 days. The acellular scaffold group showed a delayed healing response compared to other groups, while cellular+BMP2 scaffold showed decreased mechanical properties. Bone mineral density (BMD) was not significantly different among groups.

Chen *et al*.[41] in 2015 investigated the efficacy of the injection of human ADSCs in type II collagenase-induced rotator cuff injuries in 120 rats. Among the 120 animals, 12 with a healthy supraspinatus tendon were evaluated at day 0 and among the 108 left, 60 underwent a saline infusion as the placebo group and 48 underwent human ADSCs injection. The supraspinatus tendon of both limbs was subjected to biomechanical and histological analysis at 7, 14, 21 and 28 days after collagenase injection. The appearance of the supraspinatus tendons was assessed over time in both the control and the ADSCs-injection group and the presence of severe bleeding and inflammation was assessed at day 7. A significant recovery of the appearance of the supraspinatus tendon was assessed in both groups at day 28. The histological analysis, which was performed on the supraspinatus tendon of the right limb, already revealed neater and more parallel fiber arrangement in the ADSCs-injection group compared to the control at day 7. At day 28, the histological analysis assessed the absence of inflammatory cells and the structural integrity of the tendon cell morphology in both groups. Furthermore, the biomechanical tests, which were performed on the left limb, revealed a higher tensile strength of the injured tendons with treatment compared to the control group on day 7. However, the tensile strength was similar on days 21 and 28. Although, no statistical difference was presented in the biomechanical and histological analysis between the ADSCs and the control group at 28 days, an improvement on the tensile strength was found to be significantly enhanced at day 7.

Canapp *et al*.[42] in 2016 reported clinical findings for dogs diagnosed with supraspinatus tendinopathy treated with an ultrasound guided injection of a combination of ADSCs and platelet-rich plasma. Efficacy of the treatment was evaluated through a gait analysis at 90 days of follow up and subsequent ultrasounds. Results showed significant improvements after treatment, thus suggesting a positive effect.

Eliasberg *et al*.[43] in 2017 analyzed the histological changes in rotator cuff muscle fibers in 90 mice after injections of perivascular stem cells (PSCs) harvested from adipose tissue. Mice were assigned to 1 of 3 surgical procedures: sham, supraspinatus and infraspinatus tendon transection (TT), or TT and denervation via suprascapular nerve transection(TT+DN). Mice received no injection, injection with saline solution, or injection with pericytes or adventitial cells either at the time of the index procedure ("prophylactic") or at 2 weeks following the index surgery ("therapeutic"). Muscle were harvested at 6 weeks and a significant reduction in muscle atrophy was found in the mice treated with PSCs compared with the respective controls.

Rothrauff *et al*.[44] in 2019 investigated the effect of ADSCs and transforming growth factor-ß3 (TGF- ß3) on enthesis

healing after repair of massive RCTs in rats. A total of 48 animals underwent bilateral transection of the supraspinatus and infraspinatus tendons with intramuscular injection of botulinum toxin A. Twenty-four rats underwent acute tendon transection and immediate application of 1 of 8 interventions: (1) no repair, (2) repair only, or repair augmented with (3) fibrin, (4) GelMA, (5) fibrin + ADSCs, (6) GelMA + ADSCs, (7) fibrin + ADSCs + TGF-β3, or (8) GelMA + ADSCs + TGF-β3. The remaining rats received same interventions after 8 weeks, thus simulating a chronic tear. Bone mineral density and histologic appearance were evaluated 4 weeks after the repair. Bone mineral density of the proximal humerus was higher in repairs of chronic tears augmented with fibrin+ADSCs and GelMA+ADSCs than in unrepaired chronic tears. No differences in histologic features were found. Furthermore, the supplementation of TGF- ß3 to ADSCs did not add significant benefits. This results suggest that tear chronicity may mediate the efficacy of cell-based therapies.

Wang *et al*.[45] in 2019 studied the effect of exosomes isolated from human ADSCs on histologic and biomechanical properties in a rat model of a massive rotator cuff tear. A bilateral supraspinatus and infraspinatus tenotomy was performed on 42 rats. They were randomly assigned to 3 groups: the sham surgery group, the saline group (treated with a saline injection), and the ADSCs-Exos group. A histological analysis was performed at 8 and 16 weeks of follow-up. The ADSCs-Exos group showed decreased atrophy, fatty infiltration, inflammation, and vascularization of muscles. Furthermore, the ADSCs-Exos-treated rotator cuffs had better biomechanical properties than those in the saline-treated group.

In conclusion, starting from 2014, these studies have tried to implement the prosthetic design and the use of ADSCs, from the simple use of injections of ADSCs until the use of ADSCs with TGF-β3 or the use of exosome improving the objectives and the different purposes and leading to better results than previous studies. Probably an increasingly specific and accurate use of ADSCs could lead to more specific and better results, as in the case of the study on muscle atrophy through the specific use of the exosome.

Clinical evidence

Regarding the application of ADSCs in shoulder pathologies in human, only two clinical studies have been published so far.[46,47] Kim *et al*.[46] in 2017 investigated clinical and magnetic resonance imaging (MRI) outcomes following rotator cuff repair augmented with an injection of ADSCs loaded in fibrin glue. In their study, two groups composed of 35 patients each were compared: 35 patients received an injection during surgery (a mean of $4.46x10^6$ stem cells in 2 mL of fibrin glue), while the other 35 did not receive any injection and were used as matched controls based on sex, age, and lesion size. At 2 years postoperatively, both groups showed significant clinical improvements compared with preoperative levels. However, no differences could be found between the 2 groups for pain (VAS), range of motion, as well as Constant and UCLA scores. From a radiological standpoint, the ADSCs injection group showed a significant lower retear rate (14.3%) compared with the control group (28.5%) on magnetic resonance imaging (MRI) at 1-year follow-up.

Jo *et al*.[47] in 2018 reported a clinical study on the effect of an intratendinous injection of low- mid- and high- dose autologous ADSCs at 6 months of follow-up in patients with partial-thickness RCTs. In 2019 they reported the results of the same study after 2 year of follow-up.[48] Patients suffered from shoulder pain for at least seven months without a history of shoulder surgery. MRI examination before injection identified four articular-side tears (21%), 14 bursal-side tears (74%), and three intratendinous tears (16%). The first part of the study consisted of 3 dose-escalation cohorts; low- ($1.0x10^7$ cells), mid- ($5.0x10^7$ cells), and high-dose ($1.0x10^8$ cells) with 3 patients in each cohort for the evaluation of the safety and tolerability. The second part of the study included 9 patients receiving the high-dose for the evaluation of the exploratory efficacy. Patients were followed up at 1, 3, 6, 12 and 24 months after injection. High concentration injection resulted in a reduction of 71% of shoulder pain (VAS), whereas high- and mid- dose injection resulted in improved Constant-Murley score (27% and 20% respectively) and SPADI score (80% and 77% respectively). At the MRI conducted 6 months after treatment, up to 90% reduction in the bursal-sided defect was shown. No adverse events were noticed. In 2019,[48] the authors showed that at 1 year follow up the SPADI scores significantly decreased by 77.3%, 87.0%, and 80.8% in the low-, mid- and high-dose group respectively. At 2 years follow up further improvement in the SPADI score were noticed as means of 85.5%, 91.5%, and 90.2% in the low-, mid- and high-dose group respectively. Accordingly, the Constant score significantly increased by 32.2% and 32.9% at 1 year, and by 38.6% and 44.2% at 2 years, in the mid- and high-dose groups respectively. The bursal-side defect on MRI decreased by 96.8% at 1 year and 100.0% at 2 years in the high-dose group.

In conclusion, according to the results of both studies, the possibility of inducing neo-tissue formation in a partial rotator cuff defect without surgery seemed promising.[47,48]

Future directions

The application of biological agents in the treatment of shoulder pathologies is rapidly evolving as new technologies emerge. The chronic changes and poor healing capacity make the rotator cuff an especially appealing target for biologic agents. However, these agents have become increasingly popular despite a relative dearth of clinical data to support their use.

While most of the animal studies have shown positive benefit in the injection of ADSCs in RCTs, only few clinical studies have been published on humans. According to the aforementioned *in vivo* studies, the injection of ADSCs in RCTs has been found to improve the fiber pattern and increase the fiber strength, decrease the local inflammation and the muscle atrophy. Promising results, such as a decrease in re-tearing rate, a reduction in pain and an enhancement in the neo-tissue induction, have been reported in human clinical trials too.

In the future, long term studies to examine the cost-effectiveness and the predictability of results compared to the standard conservative and surgical treatment should be assessed before introducing the ADSCs as an effective and viable option in the treatment of RCTs in the daily practice.

Conclusions

The application of ADSCs represents a promising methodology in the treatment of RCTs. Basic science evidence as well as preliminary clinical data are encouraging but further clinical studies are required before drawing a definitive conclusion.

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