# Regenerative Medicine Options for Chronic Musculoskeletal Conditions: A Review of the Literature

*Sean W. Mulvaney, MD[1]; Paul Tortland, DO[2]; Brian Shiple, DO[3]; Kamisha Curtis, MPH[4]*

1 Associate Professor of Medicine, Uniformed Services University, Bethesda, MD

2 FAOASM, Associate Clinical Professor of Medicine, University of Connecticut, Farmington, CT

3 CAQSM, RMSK, ARDMS; The Center for Sports Medicine & Wellness, Glen Mills, PA

4 Regenerative and Orthopedic Sports Medicine, Annapolis, MD

## Abstract

Regenerative medicine as applied to musculoskeletal injuries is a term used to describe a growing field of musculoskeletal medicine that concentrates on evidence-based treatments that focus on and augment the body's endogenous repair capabilities. These treatments are targeted at the specific injury site or region of injury by the precise application of autologous, allogeneic or proliferative agents. Focusing on the repair of chronic musculoskeletal injuries, this paper will discuss both background and emerging theories in regenerative medicine, as well as specifically address developments in the clinically-relevant literature on specific treatments including: prolotherapy, platelet-rich plasma, autologous mesenchymal stems cells, alpha 2 macroglobin, and human tissue-derived allograft products.

**Keywords:** Regenerative medicine, platelet-rich plasma, mesenchymal stem cells, prolotherapy, micro-fragmented adipose, bone marrow concentrate, alpha 2 macroglobin

## Introduction

The term "regenerative medicine," as applied to musculoskeletal injuries, describes a rapidly growing field of musculoskeletal medicine that employs evidence-based treatments that focus on augmenting the body's endogenous repair capabilities both at the specific injury site and at the region of injury by the precise application of autologous, allogeneic or proliferative agents. World-wide, the market for regenerative medicine is expected to be over 67 billion dollars in spending on biologics and cell therapies by 2020 (1).

Specifically, regenerative medicine also stands in contrast to treatment modalities that impair the body's ability to facilitate endogenous repair mechanisms such as anti-inflammatory drugs (2,3); destructive modalities (e.g., radio frequency ablation of nerves, botulinum toxin injections) (4); and surgical methods that permanently alter the functioning of a joint, including joint fusion, spine fixation, and partial or total arthroplasty. When compared to other allopathic options (including knee and hip arthroplasty with a 90-day mortality rate of 0.7% in the Western hemisphere) (5), regenerative medicine treatment modalities have a lower incidence of adverse events with a growing body of statistically significant medical literature illustrating both their safety and efficacy (6).

When evaluating regenerative treatment options, it is reasonable to start by evaluating the medical evidence for currently accepted medical options for subacute and chronic musculoskeletal injuries.

Non-steroidal anti-inflammatory drugs (NSAIDs), as well as corticosteroid preparations, are widely prescribed for acute and chronic pain conditions. However, according to the Cochrane Database Systemic Reviews, there is poor justification in the medical literature to indicate they promote improved long-term tissue healing (7,8). NSAIDs may interfere with tissue healing (9,10). In 2017, a well-executed randomized controlled trial (RCT) with two-year follow-up comparing intra-articular injection of corticosteroids to normal saline injections for the treatment of knee osteoarthritis showed no association with improvement in pain. In addition, the steroid treated knees showed MRI evidence of accelerated osteoarthritis (11). The combination of local anesthetic and corticosteroid has substantial evidence showing that corticosteroids are toxic to chondrocytes both in vivo and in vitro (12,13). Regarding the use of corticosteroids in treating tendinopathy, in 2010 Coombes and colleagues published a meta-analysis of 41 RCTs that concluded that "at four weeks post-injection, the non-injection groups had better pain and function" (14). In addition, a randomized controlled trial

comparing corticosteroid to placebo (saline) injections demonstrated worse outcomes in the corticosteroid injection group after one year (15).

The physiologic argument for using anti-inflammatory medications for the treatment of tendinopathies was called into question, if not refuted, in a landmark publication by Kraushaar and Nirschl in 1999. Using electron microscopy sections of human lateral epicondyle tendons clinically identified as tendinitis, they demonstrated that there was a conspicuous absence of cells associated with inflammation present in what previously, and inaccurately, had been called "tendinitis" (a term implying inflammation). They successfully demonstrated that the underlying pathology, instead, represented a chronic degenerative condition referred to as "tendinosis" (16).

In the case of spine injections, including epidural steroid injections in the setting of subacute and chronic lumbar pain, an updated 2009 Cochrane review of 18 RCTs concluded "there is currently insufficient evidence to support the use of [corticosteroid] injection therapy in subacute and chronic low-back pain" (17).

Many standard orthopedic surgeries, including arthroscopic surgery for the repair of knee meniscal tears in patients over the age of 40, have been shown in a recent meta-analysis of nine RCTs to be no better than sham surgery or conservative treatment (18,19).

Opioid therapy has also long been a mainstay of treatment for chronic non-neoplastic musculoskeletal pain. However, chronic narcotic therapy has inadvertently contributed to a national epidemic of opioid-related deaths (20) in addition to the known adverse effects of opioid-induced hyperalgesia, constipation, and lack of long-term efficacy or improved quality of life (21).

These publications in high-impact peer reviewed medical journals may cause physicians treating musculoskeletal disorders to consider potential alternative treatments, including safe, physiologically sound treatment options that are supported by reasonable medical evidence.

The regenerative medicine treatment model focuses on shifting the balance from catabolism and tissue degeneration towards anabolism and tissue repair on a local and regional level. The body is capable of self-repair. In the setting of chronic injury there are several reasons for inadequate or failed self-repair:

1) The body fails to recognize an injury and mounts an effective healing response.

2) The repair mechanism is overwhelmed by ongoing tissue insults such as chronic repetitive movements without adequate recovery, ligamentous laxity resulting in pathologic joint movement, and functional movement disorders resulting in pathologic movement.

3) The repair mechanisms are inhibited by a sub-optimal healing milieu. Factors contributing to a catabolic, sub-optimal healing milieu include, but are not limited to: exposure to toxins (including many pharmaceuticals), poor diet, obesity, lack of regular exercise, chronic systemic inflammation, chronic infection, poor sleep, hormonal deficiencies, and chronic stress (22,23).

Each of these reasons for failure to self-repair is a potential target for regenerative medicine and counseling.

In addition, as we age, the body moves towards senescence with a slow shift from a balanced catabolic/anabolic environment to one that slightly favors catabolism, thus resulting in gradual tissue degeneration. At some point, this slow senescence becomes clinically manifested in the form of chronic injuries. One goal of regenerative medicine treatment is to augment the anabolic environment through the stimulation of native and natural processes.

*Dr. Sean Mulvaney performing an ultrasound-guided bone marrow aspirate concentrate injection.*

Many regenerative medicine techniques rely on precise injections of autologous, allogeneic or proliferative agents that initiate (or re-initiate) a productive healing cascade by stimulating a repair response. Often this is accomplished by initiating an acute inflammatory reaction in the target tissue. This focuses the body's ability to heal itself by providing initial injury debridement through the action of macrophages and induces the proliferative phase of tissue repair, among many other key functions (24). This inflammatory phase lasts for 10 days. This is followed by the proliferative healing phase, lasting 30 days, and that involves chemical messengers released from the injury site that recruit fibroblasts to the injury site and induce angiogenesis at the site to facilitate tissue repair. The final phase of tissue healing is the remodeling phase, during which the rapidly laid down type 3 collagen fibers are gradually replaced by stronger, more organized type 1 collagen fibers (25). This remodeling takes up to 300 days to complete.

Successful regenerative medicine treatment depends not only on an accurate diagnosis but also in large part on precise guidance of injections. Many of the injectates used in regenerative medicine are costly to prepare or purchase and ultrasound-guided application, along with detailed knowledge of sonographic anatomy, is warranted (26). It is also difficult to assess the effectiveness of therapies without knowing precisely where they were placed in or near the injured tissue. In his 2013 review of palpation-guided versus ultrasound-guided peripheral injections, Hall showed a remarkably low level of accuracy when injections are performed based on palpation-guided landmarks (27). Soft tissue structures such as ligaments, tendons, joint capsules, and muscles, should be injected using real-time ultrasound guidance. Many spine targets have reasonable medical literature supporting the use of ultrasound guidance (28,29). Fluoroscopic guidance is suitable for intervertebral disc and transforaminal epidural injections, as well as for subchondral and intraosseous injections.

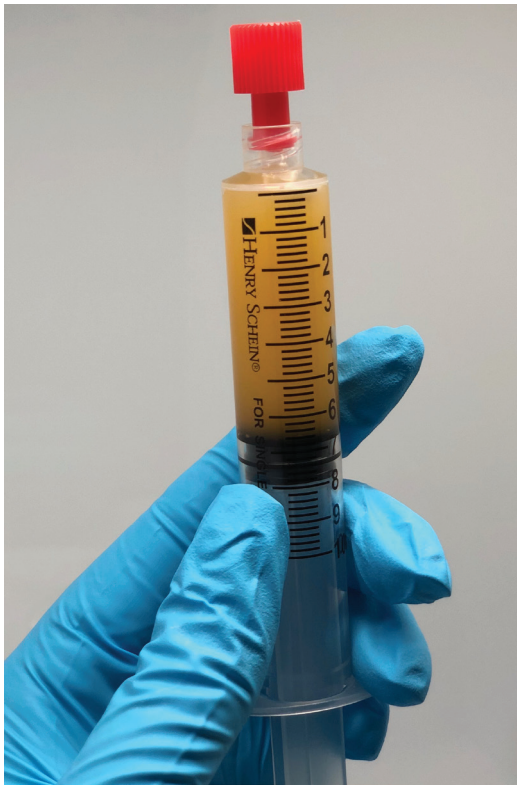
## Prolotherapy

Prolotherapy, which is a contraction of the term "proliferative therapy," has been used as a treatment modality since the 1950s. From its conceptual organization and initial publication by Hackett (30), prolotherapy has targeted chronic ligamentous laxity as the etiology of many chronic cases of joint and spine pain. The theory underlying prolotherapy states that accumulated ligament laxity (through acute trauma or chronic repetitive actions) allows the joints and spine to move beyond their intended physiologic parameters. This disproportionate motion then leads to pathologic responses such as annular ligament tears resulting in vertebral disc bulges, or cartilage degradation and osteophyte generation resulting in osteoarthritis. In typical scenarios that produce chronic pain, this slowly progressive ligamentous laxity does not induce a productive healing response. Prolotherapy has generally been used as a regional modality, insofar as many ligaments work in concert to prevent abnormal joint motion. It is also used in tendinopathies (31).

The most studied "proliferant" solution is 15% dextrose, although other agents have been used. When injected in or very proximal to a ligament or tendon, the hypertonic dextrose induces mild cellular injury via a rapid osmotic shift of fluid, which in turn initiates an inflammatory response (32). This focused initiation of the healing cascade eventually will heal the previously unrecognized ligamentous injury and restore the damaged ligament to its ideal length and structure. By healing all or most of the major ligaments in a painful joint or section of spine, normal motion parameters will be restored, allowing the area to heal over time. Because the healing cascade is initiated by induction of inflammation, patients need to refrain from using anti-inflammatory medications for seven days prior to treatment and in the post-treatment recovery period. In the cases of depo preparations of corticosteroids, usage should cease 30 days before treatment as well as during the healing process in order to achieve optimal benefit from treatment.

For years the scientific evidence supporting the use of prolotherapy lagged behind its use in clinical practice. In the last decade, however, this lack of medical evidence has been effectively addressed by dedicated researchers. High-quality studies currently support the use of prolotherapy in many chronic injuries. One of the most significant of these studies was a multi-center RCT by Rabago, Patterson, and colleagues in which the investigators followed 90 patients for one year and concluded that prolotherapy resulted in clinically meaningful improvement of pain, function, and stiffness scores for knee osteoarthritis (OA) when compared to saline injections or at-home exercise programs. The protocol used in the study targeted both intra-articular and ligament structures around the knee (33). Hauser et al. published a systematic review of dextrose prolotherapy for chronic musculoskeletal pain. Their paper reviewed

14 RCTs and concluded the "use of dextrose prolotherapy is supported for treatment of tendinopathies, knee and finger joint OA, and spinal/pelvic pain due to ligament dysfunction" (34). Dumais and colleagues conducted a randomized crossover study for the treatment of knee osteoarthritis and concluded "the use of prolotherapy is associated with a marked reduction in symptoms, which was sustained for over 24 weeks" (35). A very interesting double-blind RCT conducted by Maniquis-Smigel and colleagues looked at the analgesic effect of a caudal epidural with 5% dextrose in water (D5W) in chronic low back pain. They concluded that "a caudal epidural with D5W for moderate-to-severe chronic non-surgical low back pain with radiation to either gluteal or leg areas demonstrated consistent analgesic responses and resulted in a long-term improvement in pain and disability" (36). There are now many high-quality statistically significant studies supporting the use of prolotherapy in chronic spine pain, joint osteoarthritis, and tendinopathies (37-41).



*Platelet-rich plasma ready for use.*

## PRP

Platelet-rich plasma (PRP) is defined as a concentration of platelets above baseline. It has been widely accepted that a platelet concentration of four times baseline constitutes an adequate PRP preparation. However, that dogma is now being challenged, at least for some of the reasons enumerated below.

PRP therapy has been in clinical use since the 1990s (42). PRP is prepared from autologous blood by using centrifuge density-separation and removal of the red blood cells, and then further concentrating the platelet rich fraction of the remaining plasma. Platelets activate (degranulate) when they contact air, broken fragments of collagen (such as at the site of damaged tissue) or sense another platelet in proximity undergoing degranulation. When platelets degranulate they release alpha granules that contain up to hundreds of cytokines and chemical messengers that signal for inflammation and stimulate the body's endogenous repair mechanisms.

PRP has been shown to be an effective treatment modality in many well-done RCTs (43-48), although some of the evidence had shown mixed results (49). Laver et al. published a systematic review of the literature looking at 29 studies (11 RCTs) comparing PRP against hyaluronic acid (HA) for both knee and hip OA. They concluded that current clinical evidence supports the benefit of PRP treatment for knee and hip OA compared to several alternative treatments (51).

PRP has demonstrated clinical efficacy in the treatment of lumbar discogenic pain in an RCT with one-year follow-up (52). In addition, PRP has been shown to be effective in the treatment of low back pain due to sacroiliac joint dysfunction, lumbar facet syndrome, and low back pain associated with lumbar multifidus atrophy (53-55).

Sanchez and colleagues published a study showing the efficacy of treating severe knee OA utilizing intra-articular PRP in combination with sub-chondral injection of PRP at the medial femoral condyle and the medial tibia plateau (56). This study, as well as the previously mentioned study by Rabago, illustrate an emerging concept in regenerative treatments. In the past, osteoarthritis was treated with intra-articular injections only, regardless of the injectate (corticosteroids, hyaluronic acid products, PRP, etc). However, a more comprehensive model is emerging that includes treating pathologic joints by addressing at least two of the three components: 1) the intra-articular component (cartilage surfaces and synovium); 2) the soft tissue component (stabilizing ligaments and tendons); and 3) the sub-chondral osseous component, which is how the joint cartilage is both physically supported and nourished. Addressing at least two of the joint components is physiologically compelling and gaining support in the medical literature (57,58).

One issue that continues to confound the results of many RCTs comparing the tested substance to a saline-injected control is that there is reasonable evidence indicating that a saline injection is not a control but a treatment (59). Another confounding

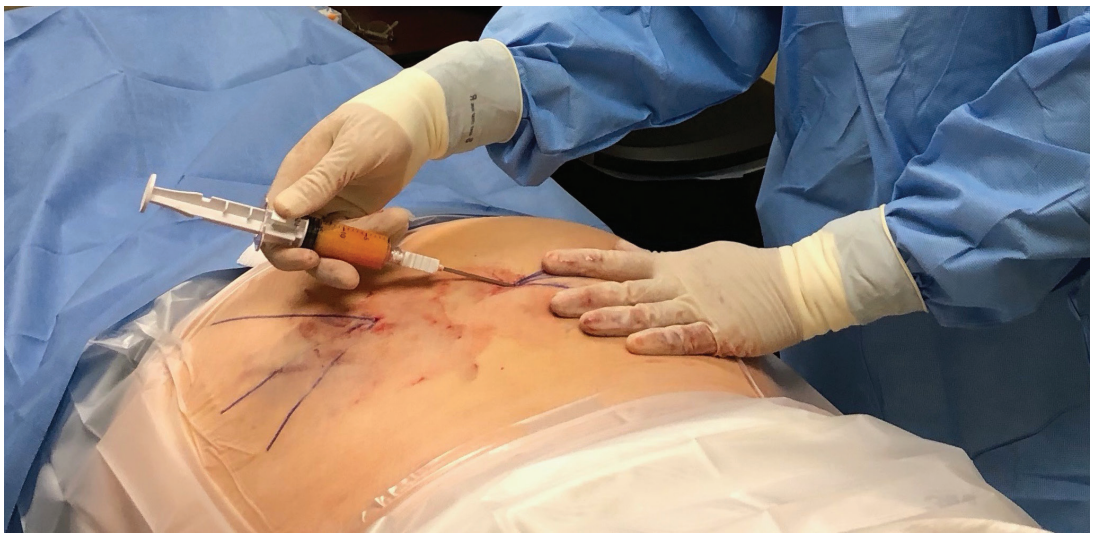
issue in PRP research may be attributed to the fact that it is difficult to statistically account for, and to appropriately power studies for, variations in even similar types of injuries, post-treatment recovery regimes, method of injection, skill of the clinician, and concomitant pharmaceutical use (and many other factors). Also, there is not one homologous preparation of PRP that is being compared in the literature (60). There are many commercially available systems and lab-based preparation protocols for the preparation of PRP. For example, there are leukocyte-rich and leukocyte-poor preparations, to name just one of the variables. Even if the method of PRP preparation is standardized, each individual patient starts with a different native baseline platelet count, resulting in a wide variety of final platelet concentrations within each PRP preparation, such that there is significant variability in the number of platelets per microliter injected even when employing the same preparation method. Furthermore, optimal platelet concentrations have not been established for musculoskeletal repair. A general rule is that 4-5 times concentration over baseline is a reasonable goal for a PRP preparation method. However, absolute platelet count per microliter is a more accurate method of comparison.

The qualitative differences in PRP also is a confounding variable in research. The presence and concentrations of the various blood components—RBCs, WBCs, and platelets—all have been proposed to have either beneficial or deleterious effects. For example, there is some data to support that leukocyte-poor PRP is more beneficial than leukocyte-rich PRP for intra-articular applications, while leukocyte-rich PRP may be superior for intra-tendon applications (61,62). Nonetheless, the clinical superiority of any one preparation has not been established in the medical literature and remains the subject of ongoing research (63). Few studies investigating the use of PRP actually document the qualitative nature of the PRP being injected. Mautner et al. gave us a comprehensive PRP nomenclature paper designed to define PRP based on the variable components to accurately and quickly describe the type of PRP being used in the prospective study (64).

Is PRP better than prolotherapy? There are only a few studies comparing the two modalities. In a double-blind RCT comparing 7 ml of intra-articular PRP and 7 ml of 25% dextrose, both groups had statistically significant improvement over six months. However, the PRP group was associated with greater improvement in their WOMAC scores (65). In a meta-analysis of 18 RCTs comparing injection therapies for the treatment of rotator cuff tendinopathy, both PRP and prolotherapy had statistically significant superiority over corticosteroids, NSAIDs, hyaluronic acid, and botulinum toxin at 24 weeks (66).

## Autologous Mesenchymal Stem Cells

Autologous mesenchymal stems cells (MSCs) appear to facilitate musculoskeletal repair not so much by differentiating into the required target tissue but by binding to the injury site and acting in a paracrine fashion to facilitate tissue repair (67). Autologous stem cell preparations can be sourced from adipose derived MSCs and from bone marrow derived MSCs. Currently there is ongoing debate regarding which source is more optimal for musculoskeletal applications. Marrow-derived



*Dr. Sean Mulvaney harvesting adipose as a source of mesenchymal stem cells.*

stem cells have been shown to have a higher osteogenic and chondrogenic potential with in vitro studies. But human studies investigating the use of adipose-derived stem cells for the treatment of osteoarthritis have shown comparable results to those for marrow-derived treatments. Furthermore, adipose has a significantly greater number of stem cells than bone marrow per equivalent unit of measurement. In addition, as we age, the population of stem cells in the bone decreases precipitously while it remains relatively stable in the adipose. Finally, adipose-derived stem cells appear to maintain their regenerative properties more than bone marrow derived MSCs as we age (68). However, it remains to be seen whether any of these differences result in clinically meaningful differences in treatment outcomes insofar as both forms of treatment—adipose-derived and bone marrow-derived—appear to produce improved outcomes in human studies.

At the time of writing this, the U.S. Food and Drug Administration (FDA) is permitting bone marrow aspiration and centrifugation separation of bone marrow to density-select the nucleated cell layer and micro-fragmented adipose preparations. The FDA has not approved any technique that isolates the stromovascular fraction (SVF) from adipose tissue using enzymatic digestion of the extracellular matrix. Currently the FDA does not allow for culture expansion of harvested stem cells; this technique would exceed the FDA mandate of avoiding "more than minimal manipulation" of harvested autologous mesenchymal or hematopoietic stem cells. All preparations of autologous stem cells must be reinjected in the donor-patient on the same day as harvesting (69).

A review of the medical literature found six RCTs using bone marrow and adipose-derived stem cells to treat knee arthritis which concluded the following: there were no serious adverse events and there were superior radiological outcomes favoring stem cell injections. Two trials reported improved histological outcomes, improved arthroscopically-scored healing rates, and superior patient-reported outcomes. However, the level of evidence in some of the studies was reduced to level 3 due to perceived risk of bias (70). Emadenin et al. published a randomized, triple-blind, placebo-controlled trial using BMAC for knee OA of 43 patients and concluded that BMAC was safe and provided clinically significant relief of pain for over six months versus placebo (71).

Centeno and colleagues published a study of 840 OA knees with long-term follow-up treated with bone marrow derived stem cells and found this application to be both safe and efficacious (72). Centeno and colleagues also published a prospective multi-site study of 115 shoulder OA and rotator cuff tears treated with bone marrow derived stem cells which showed statistically significant improvement in DASH scores (73). Michalek and colleagues published a multi-center case control study of 1,114 patients with knee and hip OA treated with adipose-derived stem cells. At 12 months after treatment there was a 75% improvement in 63% of patients and at least a 50% score improvement in 91% of patients. There were no serious adverse effects associated with either the treatment or at the small volume adipose harvest sites (74). Hernigou et. al. recently published their landmark RCT comparing total knee arthroplasty (TKA) with subchondral bone marrow injections for severe knee OA, with a 12-year follow-up. Both groups had similar favorable improvement. The cell therapy group showed improvement in both cartilage and bone marrow lesions. There were significantly greater medical and surgical complications following TKA compared to the cell injection group (75). Hernigou and colleagues also pioneered the technique of a BMAC treatment for avascular necrosis (AVN). Using percutaneous injections into the necrotic area of femoral heads, they demonstrated both safety and clinical efficacy for this condition which is otherwise treated with hip core decompression and eventually total hip arthroplasty (76,77). Pettine and colleagues published a study with 3-year follow-up which showed safety and significant efficacy using BMAC injections in lumbar intervertebral discs with symptomatic annular tears to treat lumbar discogenic pain with a VAS improvement of 71% and an ODI improvement of greater than 64% (78). Hernigou also published a landmark rotator cuff repair study with 10-year follow-up comparing surgically repaired rotator cuff tears with and without BMC augmentation. In the BMAC augmented rotator cuff repairs BMAC was surgically placed in the repair site as well as the subchondral foot print of the rotator cuff repair site. There were 45 patients in each group. At six months 100% of the BMC augmented repairs showed MRI and U/S evidence of healing, whereas the repair-only group showed 67% healing. At 10-year follow-up, the BMC augmented group showed 84% were still healed versus only 44% of the repair-only group (79). Gobbi et al., in his landmark work on osteochondral defect repair in the knee, prospectively treated 15 patients with large

chondral defects with a type I/III collagen matrix seeded with autologous BMC and sealed with fibrin glue as a single stage dry arthroscopic procedure. This resulted in significant improvement in patient outcome scores, MRI evidence of healing, and second look arthroscopy showing normal to near normal hyaline like cartilage in over 80% of the subjects (80).

Russo and colleagues published a retrospective observational study of 30 patients treated with autologous micro-fractured adipose for knee OA. They concluded the treatment was successful, with significant improvement in VAS, KOOS, and IKDC scores, and that it was both safe and compliant with current regulations (81). Striano and colleagues published a case series of 18 shoulders with OA and or rotator cuff tears treated with micro-fragmented adipose and concluded, after a one-year follow-up, that there was significant improvements in pain, function, and quality of life (82). Although there is ongoing debate about which source of MSCs is superior for orthopedic regenerative applications, both need further high quality RCT level evidence to support their clinical efficacy.

The Australasian College of Sports Physicians published a position statement in 2015 stating that autologous MSC stem cell therapy should have the same 4 phase trial safety testing as a new drug before being considered safe. This seems to be an onerous standard for a person's own, non-culture expanded cells. However their position statement was also covering potential use of culture expanded MSCs (83). Nonetheless, currently there are no reports of non-expanded or culture expanded MSCs having tumorigenic potential (84). Regarding the safety of non-culture expanded MSCs from either bone marrow or adipose tissue, current medical literature supports that both sources appear to be safe and reasonably efficacious for the treatment of knee and hip osteoarthritis and some tendinopathies and tendon tears; however more high-quality research is needed.

## Alpha-2 Macroglobulin

Alpha-2 macroglobin (A2M) is a serum protease inhibitor. It is a complex molecule that sequesters and neutralizes catabolic mediators. It is found in the blood and soft tissues but it is not significantly present in joint fluid (85). A2M can be concentrated from a patient's blood and injected into an injury site. The theory and goal is to reduce the catabolic milieu around an injury location or the intra-articular environment of arthritic joints. There is only one low-level study currently supporting its clinical use. However, there is an interesting animal study by Wang and colleagues which illustrates that A2M may have utility in ameliorating the post-traumatic arthritis associated with anterior cruciate ligament (ACL) rupture. In the event of an ACL rupture, there is an extreme intra-articular catabolic event that has been shown to induce chondrocyte apoptosis and eventual post-traumatic arthritis, even if the ACL is surgically reconstructed (86). In Wang's study, an ACL injury was induced in 60 rats, 30 of which received A2M injections, while a control group received saline injections. The A2M group did not go on to develop post-traumatic arthritis, while the saline group did. Wang concluded that "A2M is a powerful inhibitor of many cartilage catabolic factors and that it can attenuate posttraumatic OA cartilage degeneration" (87). Although making treatment decisions based on animal studies is sub-optimal, there is not a currently accepted treatment for reducing the post-traumatic arthritis seen in ACL injuries. A2M is an autologous and safe option which may prove to have significant clinical utility in reducing the development of post-traumatic arthritis in the setting of intra-articular trauma.

## Other Human Tissue-Derived Allograft Products

Allograft products used in regenerative medicine consist of donated human placental and amniotic tissue derived allografts and components of umbilical cord blood mesenchymal stem cells, including the isolated exosomes of these cells. These products do not contain viable MSCs. Although these products have a few clinical level-4 studies published which show initial safety and potential use for musculoskeletal injuries, overall, they lack the published medical evidence to demonstrate efficacy (88-91), and they are generally expensive to administer. Allograft products may be a reasonable option, especially for patients with contraindications to other regenerative autologous options, such as a of history blood or bone marrow cancers.

## Conclusions

Regenerative medicine treatments for chronic musculoskeletal conditions have a growing body of medical evidence supporting both their safety and their efficacy in clinical application in joints, spine, ligaments, tendons and vertebral discs. Prolotherapy and PRP have reasonable RCT level clinical evidence supporting their safety and efficacy. Autologous non-culture

expanded mesenchymal stem cells, whether adipose or bone marrow derived, appear to be safe, and the initial body of medical evidence show promise as a therapy to improve pain and function in chronic musculoskeletal maladies. Allograft regenerative medicine products have only few level-4 clinical studies supporting their clinical application and require more unbiased published literature to make any recommendation on their use. The term "regenerative medicine" may imply true tissue regeneration, but this has not been validated in the literature. Instead, the term regenerative medicine can be associated with enhancement (through relative reduction of catabolic factors) or activation of endogenous healing mechanisms. The efficacy and safety of regenerative medicine techniques should be thoughtfully balanced against the same considerations when employing many currently accepted therapies, including both surgical and non-surgical options. There is real, quantifiable mortality associated with arthroplasty (5,000 deaths per year in the U.S. alone) (92) and significant morbidity associated with NSAID and corticosteroid use. In similar medical literature reviews, it is both common and academically prudent to comment that "further high-quality research is needed." While this is certainly a true statement, there is enough medical evidence to both critically re-evaluate many currently accepted therapies and consider some regenerative options to help both reduce pain and return patients to movement.

## REFERENCES


1. World Regenerative Medicines Market: Opportunities and Forecasts, 2013–2020. *Allied Market Research Report*. (2014). Retrieved from https://www.alliedmarketresearch.com/regenerative-medicines-market. Accessed 6 July 2016.

2. Kaushal M, Kutty NG, Rao CM. Nitrooxyethylation reverses the healing-suppressant effect of Ibuprofen. *Mediators Inflamm*. 2006;4:24396.

3. Su WH, Cheng MH, Lee WL. Nonsteroidal anti-inflammatory drugs for wounds: pain relief or excessive scar formation? *Mediators Inflamm*. 2010;413238.

4. Salari M, Sharma S, Jog MS. Botulinum toxin induced atrophy: an uncharted territory. *Toxins*. 2018;10(8):313.

5. Singh JA, Kundukulam BS, Riddle DL, Strand V, Tugwell P. Early postoperative mortality following joint arthroplasty: a systematic review. *J Rheum*. 2011;38(7):1507-1513.

6. Hernigou P, Auregan JC, Dubory A, Flouzat-Lachaniette CH, Chevallier N, Rouard H. Subchondral stem cell therapy versus contralateral total knee arthroplasty for osteoarthritis following secondary osteonecrosis of the knee. *Int Orthop*. 2018;42(11):2563-2571.

7. Pattanittum P, Turner T, Green S, Buchbinder R. Non-steroidal anti-inflammatory drugs for treating lateral elbow pain in adults. *Cochrane Database Syst Rev*. 2013;31(5):CD003686.

8. McLauchlan GJ, Handoll HH. Interventions for treating acute and chronic Achilles tendinitis. *Cochrane Database Syst Rev*. 2001;2:CD00232.

9. Kaushal M, Kutty NG, Rao CM. Nitrooxyethylation reverses the healing-suppressant effect of Ibuprofen. *Mediators Inflamm*. 2006;4:24396.

10. Su WH, Cheng MH, Lee WL. Nonsteroidal anti-inflammatory drugs for wounds: pain relief or excessive scar formation? *Mediators Inflamm*. 2010;413238.

11. McAlindon TE, LaValley MP, Harvey WF, et al. Effects of intra-articular triamcinolone vs saline on knee cartilage volume and pain in patients with knee osteoarthritis: a randomized clinical trial. *JAMA*. 2017;317(19):1967-1975.

12. Farkas B, Kvell K, Czompoly T, Illes T, Bardos T. Increase chondorsyte death after steroid and local anesthetic combination. *Clin Orthop Relat Res*. 2010;468(11):3112-20.

13. Dragoo JL, Danial CM, Braun HJ, Pouliot MA, Kim HJ. The chondrotoxicity of single-dose corticosteroids. *Knee Surg Sports Traumatol Arthrosc*. 2012;20(9):1809-14.

14. Coombes BK, Bisset L, Vicenzino B. Efficacy and safety of corticosteroid injections and other injections for management of tendonopathy: a systematic review of randomized controlled trials. *Lancet*. 2010;376:1751-67.

15. Coombes BK, Bisset L, Brooks P, Khan A, Vicenzino B. Effect of corticosteroid injection, physiotherapy or both on clinical outcomes in patients with unilateral lateral epicondylalgia: a randomized controlled trial. *JAMA*. 2013;309(5):461-469.

16. Kraushaar BS, Nirschl RP. Tendinosis of the elbow (tennis elbow). Clinical features and findings of histological, immunohistochemical, and electron microscopy studies. *J Bone Joint Surg Am*. 1999;81(2):259-78.

17. Staal JB, deBie RA, de Vet HC, Hildebrandt J, Nelemans P. *Spine*. 2009;34(1):49-59.

18. Lee DY, Park YJ, Kim HJ, Nam DC, Park JS. Arthroscopic meniscal surgery versus conservative management in patients aged 40 years and older: a meta-analysis. *Arch Ortho and Trauma Surg*. 2018;138(12):1731-1739.

19. Siemieniuk RAC, Harris IA, Agoritsas T, et al. Arthroscopic surgery for degenerative knee arthritis and meniscal tears: a clinical practice guideline. *Brit J Sports Med*. 2018;52:313.

20. Nuckols TK, Anderson L, Popescu I, Diamant AL, Doyle B, et al. Opioid prescribing: a systematic review and critical appraisal of guidelines for chronic pain. *Ann Intern Med.* 2014;160(1):38-47.

21. Chaparro LE, Furlan AD, Deshpande A, Mailis-Gagnon A, Atlas S, Turk DC. Opioids compared to placebo or other treatments for chronic low-back pain. *Cochrane Database Syst Rev*. 2013;8:CD004959.

22. Anderson K, Hamm RL. Factors that impair wound healing. *J Am Col Clin Wound Spec*. 2014;4:84-91.

23. Gosling CM, Forbes AB, Gabbe BJ. Health professionals perceptions of musculoskeletal injury and injury risk factors in Australian triathletes: a factor analysis. *Phys Ther Sport*. 2013;14(4):207-12.

24. Kharraz Y, Guerra J, Mann CJ, Serrano AL, Munoz-Canoves P. Macrophage plasticity and the role of inflammation in skeletal muscle repair. *Mediators Inflamm*. 2013;491497.

25. Sasaki K, Yamamoto N, Kiyosawa T, Sekido M. The role of collagen arrangement change during tendon healing demonstrated by scanning electron microscopy. *J Electron Microsc*. 2012;61(5):327-34.

26. Sibbitt WL, Peisajovich A, Michael AA, Park KY, Sibbitt RR, et al. Does sonographic needle guidance affect the clinical outcome of intraarticular injections? J *Rheumatol*. 2009;36:1892-902.

27. Hall MD. The accuracy and efficacy of palpation versus image-guided peripheral injections in sports medicine. *Curr Sports Med Rep*. 2013;12(5):296-303.

28. Yun DH, Kim HS, Yoo SD, Kim DH, Chon JM, et al. Efficacy of ultrasound-guided injections in patients with facet syndrome of the low lumbar spine. *Ann Rehab Med*. 2012;36:66-71.

29. Galiano K, Obwegeser AA, Bodner G, Freund M, Maurer H, et al. Ultrasound guidance for facet joint injections in the lumbar spine: a computed tomography-controlled feasibility study. *Anesth Analg*. 2005;101:579-83.

30. Hackett GS. (1958). *Ligament and tendon relaxation*. 3rd ed. Springfield, IL: Charles C. Thomas.

31. Yelland MJ, Sweeting KR, Lyftogt JA, et al. Prolotherapy injections and eccentric loading exercises for painful Achilles tendinosis: a randomized trial. *Brit J Sports Med*. 2011;45:421-428.

32. Jensen KT, Rabago DP, Best TM, Patterson JJ, Vanderby R. Early inflammatory response of knee ligaments to prolotherapy in a rat model. *J Orthop Res*. 2008;26(6):816e823.

33. Rabago D, Patterson JJ, Mundt M, Kijowski R, Grettie J, et al. Dextrose prolotherapy for knee osteoarthritis: a randomized controlled trial. *Ann Fam Med*. 2013;11(3):229-37.

34. Hauser RA, Lackner JB, Steilen-Matias D, Harris DK. A systematic review of dextrose prolotherapy for chronic musculoskeletal pain. *Clin Med Ins*. 2016;9:139-159.

35. Dumais R, Benoit C, Dumais A, et al. Effect of regenerative injection therapy on function and pain in patients with knee osteoarthritis: a randomized crossover study. *Pain Med*. 2012;13:990-999.

36. Smigel L, Reeves KD, Lyftogt J, Rabago D. Analgesic effect of caudal 5% dextrose in water in chronic low back pain. *Arch Phys Med Rehab*. 2015;96:10.

37. Shashank D, Sobel AD, DaSilva MF, Akelman E. Utility of prolotherapy for upper extremity pathology. *J Hand Surg Am*. 2018. In press.

38. Watson JD, Shay BL. Treatment of chronic low-back pain: a 1-year or greater follow up. *J of Alt Comp Med*. 2010;16(9):951-958.

39. Kim WM, Lee HG, Jeong CW, et al. A randomized controlled trial of intra-articular prolotherapy versus steroid injection for sacroiliac joint pain. *J Alt Comp Med*. 2010;16(12):1285-1290.

40. Yelland MJ, Sweeting KR, Lyftogt JA, et al. Prolotherapy injections and eccentric loading exercises for painful Achilles tendinosis: a randomized trial. *Brit J Sports Med*. 2011;45:421-428.

41. Ryan M, Wong A, Taunton J. Favorable outcomes after sonographically guided intratendinous injection of hyperosmolar dextrose for chronic insertional and midportion Achilles tendinosis. *AJR*. 2010;194(4):1047:53.

42. Marx RE, Garg AK. (2005). *Dental and craniofacial applications of platelet-rich plasma*. Carol Stream, IL: Quintessence Publishing Co, Inc.

43. Smith PA. Intra-articular autologous conditioned plasma injections provide safe and efficacious treatment for knee osteoarthritis: an FDA-sanctioned, randomized, double-blind, placebo-controlled clinical trial. *Am J Sports Med*. 2001;45:421-428.

44. Dai WL, Zhou AG, Zhang H, Zhang J. Efficacy of platelet-rich plasma in the treatment of knee arthritis: a meta-analysis of randomized controlled trials. *Arthro*. 2017;33(3):659-670.

45. Peerbooms JC1, Sluimer J, Bruijn DJ, Gosens T. Positive effect of an autologous platelet concentrate in lateral epicondylitis in a double-blind randomized controlled trial: platelet-rich plasma versus corticosteroid injection with a 1-year follow-up. *Am J Sports Med*. 2010;38(2):255-62.

46. Gosens T1, Peerbooms JC, van Laar W, den Oudsten BL. Ongoing positive effect of platelet-rich plasma versus corticosteroid injection in lateral epicondylitis: a double-blind randomized controlled trial with 2-year follow-up. *Am J Sports Med*. 2011;39(6):1200-8.

47. Mishra AK, Skrepnik NV, Edwards SG, Jones GL, Sampson S, et al. Efficacy of platelet-rich plasma for chronic tennis elbow: a double-blind, prospective, multicenter, randomized controlled trial of 230 patients. *Am J Sports Med*. 2014;42(2):463-71.

48. Laudy AB, Bakker EW, Reders M, Moen MH. Efficacy of platelet-rich plasma injections in osteoarthritis of the knee: a systematic review and meta-analysis. *Brit J Sports Med*. 2015;49:657-672.

49. Yerlikaya M, Taly Calis H, Sutbeyaz S, Sayan H, Ibis N. Comparison of effects of leukocyte-rich and leukocyte-poor platelet-rich plasma on pain and functionality in patients with lateral epicondylitis. *Arch Rheumatol*. 2018;33(1):73-79.

50. Laver L, Marom N, Dnyanesh L, Omer MD, Espregueira-Mendes J, Gobbi A. PRP for degenerative cartilage disease: a systematic review of clinical studies. *Cartilage*. 2017;8(4)341-364.

51. Ibid.

52. Tuakli-Wosornu YA, Terry A, Boachie-Adjei K, et al. Lumbar intradiskal platelet-rich plasma (PRP) injections: a prospective, double-blind, randomized controlled study. *PM R*. 2016;8(1):1-10.

53. Wu J, Du Z, Lv Y, Zhang J, Xiong W, Wang R, Liu R, Zhang G, Liu Q. A new technique for the treatment of lumbar facet joint syndrome using intra-articular injection with autologous platelet rich plasma. *Pain Physician*. 2016;19(8):617-625.

54. Singla V, Batra YK, Bharti N, Goni VG, Marwaha N. Steroid vs platelet-rich plasma in ultrasound-guided sacroiliac joint injection for chronic low back pain. *Pain Pract*. 2017;17(6):782-791.

55. Hussein M, Hussein T. Effect of autologous platelet leukocyte rich plasma injections on atrophied lumbar multifidus muscle in low back pain patients with monosegmental degenerative disc disease. *SICOT J*. 2016;2:12.

56. Sánchez M, Delgado D, Pompei O, Pérez JC, Sánchez P. Treating severe knee osteoarthritis with combination of intra-osseus and intra-articular infiltrations of platelet-rich plasma: an observational study. *Cartilage*. 2018; Feb 1:1947603518756462.

57. Ibid.

58. Rabago D, Patterson JJ, Mundt M, Kijowski R, Grettie J, et al. Dextrose prolotherapy for knee osteoarthritis: a randomized controlled trial. *Ann Fam Med*. 2013;11(3):229-37.

59. Bar-Or D, Rael LT, Brody EN. Use of saline as a placebo in intra-articular injections in osteoarthritis: potential contributions to nociceptive pain relief. *Op Rheum J*. 2017;11:16-22.

60. Mautner K, Malanga GA, Smith J, Shiple B, Ibrahim V, et al. A call for standard classification system for future biologic research: the rationale for new PRP nomenclature. *PM R*. 2015;7(4 suppl):S53-9.

61. Xu Z, Yin W, Zhang Y, Qi Y, Chen Y, et al. Comparative evaluation of leukocyte- and platelet rich plasma and pure platelet-rich plasma for cartilage regeneration. *Sci Rep*. 2017;7:43301.

62. Zhou Y, Zhang J, Wu H, Hogan MV, Wang J. The differential effects of leukocyte-containing and pure platelet-rich plasma (PRP) on tendon/progenitor cells; implications of PRP application for the clinical treatment of tendon injuries. *Stem Cell Res Ther*. 2015;6(1):173.

63. Andia I, Martin JI, Maffulli N. Advances with platelet rich plasma therapies for tendon regeneration. *Expert Op on Biologic T*. 2018;18(8).

64. Mautner K, Malanga G, Smith J, et al. A call for a standard classification system for future biologic research: the rationale for a new PRP nomenclature. *Am J Phys Med Rehab*. 2015;7(4):S53-S59.

65. Rahimzadeh P, Imani F, Faiz SH, Entezary SR, Narimani M. The effects of injecting intra-articular platelet-rich plasma or prolotherapy on pain score and function in knee osteoarthritis. *Clinical Int Aging*. 2018;13:73-79 .

66. Lin MT, Chiang CF, Wu CH, Huang YT, Tu YK, et al. Comparative effectiveness of injection therapies in rotator cuff tendinopathy: a systematic review, pairwise and network meta-analysis of randomized controlled trials. *Arch PM R*. 2018;10.1016/j. apmr.2018.06.028.

67. Caplan AI. Why are MSCs therapeutic? New data: new insight. *J Path*. 2009;217(2):318-24.

68. Beane O, et al. Impact of aging on the regenerative properties of bone marrow-, muscle-, and adipose-derived mesenchymal stem/stromal cells. *PloS One*. 2014;9(12).

69. United States Food and Drug Administration. Regulatory considerations for human cells, tissues, and cellular and tissue-based products: minimal manipulation and homologous use. Retrieved from https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-bio- gen/documents/document/ucm585403. pdf. Accessed February 15, 2018.

70. Pas HI, Winters M, Haisma HJ, Koenis MJ, Tol JL, Moen MH. Stem cell injections in knee oastoarthritis: a systematic review of the literature. *Brit J Sports Med*. 2017;51(15):1125-1133.

71. Emadedin M, Labibzadeh N, Liastani MG, Karimi A, Jaroughi N, et al. Intra-articular implantation of autologous bone marrow-derived mesenchymal stromal cells to treat knee osteoarthritis: a randomized, triple-blind, placebo-controlled phase ½ clinical trial. *Cryotherapy*. 2018;0001-9. In press.

72. Centeno CJ, Pitts J, Al-Sayegh H, Freeman M. Efficacy of autolo- gous bone marrow concentrate for knee osteoarthritis with and without adipose graft. *Biomed Res Int*. 2014;2014:370621.

73. Centeno CJ, Al-Sayegh H, Bashir J, Goodyear S, Freeman MD. A prospective multi-site registry study of a specific protocol of autologous bone marrow concentrate for the treatment of shoulder rotator cuff tears and osteoarthritis. *J Pain Research*. 2015;8:269-276.

74. Michalek J, Moster R, Lukac L, et al. Autologous adipose tissue- derived stromal vascular fraction cells application in patients with osteoarthritis. *Cell Transplant*. 2015;8:117-124.

75. Hernigou P, Auregan JC, Dubory A, Flouzat-Lachaniette CH, Chevallier N, Rouard H. Subchondral stem cell therapy versus contralateral total knee arthroplasty for osteoarthritis following secondary osteonecrosis of the knee. *Int Orthop*. 2018;42(11):2563-2571.

76. Hernigou P, Manicom O, Poignard A, Nogier A, Filippini P, De Abreu L. Core decompression with marrow stem cells. *Oper Tech Orthop*. 2004;14(2):68-74.

77. Hernigou P, Zilber S, Filippini P, Rouard H, Mathieu G, Poignard A. Bone marrow injection in hip osteonecrosis. *Tech Orthop.* 2008;23(1):18-25.

78. Pettine KA, Suzuki RK, Sand TT, Murphy MB. Autologous bone marrow concentrate intradiscal injection for the treatment of degenerative disc disease with three-year follow up. *Int Orthop*. 2017;41(10):2097-2103.

79. 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.

80. Gobbi A, Karnatzikos G, Scotti C, Mahajan V, Mazzucco L, Grigolo B. One-step cartilage repair with bone marrow aspirate concentrated cells and collagen matrix in full-thickness knee cartilage lesions: results at 2-year follow-up. *Cartilage*. 2011;2(3):286-299.

81. Russo A, Condello V, Madonna V, Guerriero M, Zori C. Autologous and micro-fragmented adipose tissue for the treatment of diffuse degenerative knee osteoarthritis. *J Exp Orthop*. 2017;4(1):33.

82. Striano RD, Malanga GA, Bilbool N, Azatullah K. Refractory shoulder pain with osteoarthritis, and rotator cuff tear, treated with micro-fragmented adipose tissue. *J Ortho Spine and Sports Med*. 2018;2(1):014.

83. Osborne H, Anderson L, Burt P, Young M, Gerrard D. Australasian College of Sports Physicians position statement: the place of mesenchymal stem/stromal cell therapies in sport and exercise medicine. *Brit J Sports Med*. 2016;50:1237-1244.

84. Peeters CM, Lejis MJ, Reijman M, et al. Safety of intra-articular cell-therapy with culture expaned stem cells in humans; a systematic literature review. *Osteoarthritis Cartilage*. 2013;21:1465-73.

85. Wang S, Wei X, Zhou J, Zhang J, Li K, et al. Identification of 2-macroglobin as a master inhibitor of cartilage-degrading factors that attenuates the progression of posttraumatic osteoarthritis. *Arthrit and Rheum*. 2014;66(7):1843-1853.

86. Smith TO, Postle K, Penny F, McNamara I, Mann CJ. Is reconstruction the best management strategy for anterior cruciate ligament rupture? A systematic review and meta-analysis comparing anterior cruciate ligament reconstruction versus non-operative treatment. *Knee*. 2014;21(2):462-70.

87. Wang S, Wei X, Zhou J, Zhang J, Li K, et al. Identification of 2-macroglobin as a master inhibitor of cartilage-degrading factors that attenuates the progression of posttraumatic osteoarthritis. *Arthrit and Rheum*. 2014;66(7):1843-1853.

88. Zhang S, Chuah SJ, Lai RC, Hui JHP, Lim SK, Toh WS. MSC exosome mediate cartilage repair by enhancing proliferation, attenuating apoptosis and modulating immune reactivity. *Biomaterials*. 2018;156:16-27.

89. Werber B. Amniotic tissues for the treatment of chronic plantar fasciosis and Achilles tendinosis. *J Sport Med*. 2015;219896. Epub 2015 Sep 27.

90. Lullove E. A flowable placental tissue matrix allograft in lower extremity injuries: a pilot study. *Cureus*. 2015;7(6): e275.

91. Gelhorn AC, Han A. The use of dehydrated human amnion/ chorion membrane allograft injection for the treatment of tendinopathy or arthritis: a case series involving 40 patients. *PM R*. 2017;9(12);1236-1243.

92. Singh JA, Kundukulam BS, Riddle DL, Strand V, Tugwell P. Early postoperative mortality following joint arthroplasty: a systematic review. *J Rheum*. 2011;38(7):1507-1513.