Regence

Medical Policy Manual Medicine, Policy No. 142

Orthopedic Applications of Stem Cell Therapy, Including Bone Substitutes Used with Autologous Bone Marrow

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Mesenchymal stem cells (MSCs) are multipotent cells (also called “stromal multipotent cells”) that possess the ability to differentiate into various tissues including organs, trabecular bone, tendon, articular cartilage, ligaments, muscle, and fat. Potential uses of MSCs for orthopedic applications include treatment of damaged bone, cartilage, ligaments, tendons, and intervertebral discs.

MEDICAL POLICY CRITERIA

Note: Use of platelet rich plasma is addressed in Medicine Policy No. 77 (see Cross References section). This policy does not apply to the use of unmanipulated bone marrow aspirate for spinal indications which may be considered medically necessary.

I. Mesenchymal stem cell therapy, including but not limited to manipulated or unmanipulated bone marrow, fat, and amnion cells, is considered **investigational** for all orthopedic applications, including but not limited to use in repair or regeneration of musculoskeletal tissue.

II. Allograft bone products containing viable stem cells are considered **investigational** for all orthopedic applications, including but not limited to demineralized bone matrix (DBM) with stem cells.

III. Synthetic bone graft substitutes that must be combined with autologous bone marrow are considered **investigational** for all orthopedic applications.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

1. Autologous Blood-Derived Growth Factors as a Treatment for Wound Healing and Other Conditions, Medicine, Policy No. 77
2. Progenitor Cell Therapy for the Treatment of Damaged Myocardium Due to Ischemia, Medicine, Policy No. 100
3. Stem-cell Therapy for Peripheral Arterial Disease, Medicine, Policy No. 141
4. Autologous Chondrocyte Implantation for Focal Articular Cartilage Lesions, Surgery, Policy No. 87

BACKGROUND

MSCs are associated with the blood vessels within bone marrow, synovium, fat, and muscle where they can be mobilized for endogenous repair, as occurs with healing of bone fractures. Stimulation of endogenous MSCs is the basis of procedures such as bone marrow stimulation (e.g., microfracture) and harvesting/grafting of autologous bone for fusion. Bone-marrow aspirate is considered to be the most accessible source and, thus, the most common place to isolate MSCs for treatment of musculoskeletal disease. However, harvesting MSCs from bone marrow requires an additional procedure that may result in donor-site morbidity. In addition, the number of MSCs in bone marrow is low, and the number and differentiation capacity of bone marrow-derived MSCs decreases with age, limiting their efficiency when isolated from older patients.

Tissues such as muscle, cartilage, tendon, ligaments, and vertebral discs show limited capacity for endogenous repair. Tissue engineering techniques are being developed to improve the efficiency of repair or regeneration of damaged musculoskeletal tissues. Tissue engineering focuses on the integration of biomaterials with MSCs and/or bioactive molecules such as growth factors. In vivo, the fate of stem cells is regulated by signals in the local 3-dimensional microenvironment from the extracellular matrix and neighboring cells. It is believed that the success of tissue engineering with MSCs will also require an appropriate 3-dimensional scaffold or matrix, culture conditions for tissue-specific induction, and implantation techniques that provide appropriate biomechanical forces and mechanical stimulation. Given that each tissue type requires different culture conditions, induction factors (e.g., signaling proteins, cytokines, growth factors), and implantation techniques, each preparation must be individually examined. The ability to induce cell division and differentiation, without adverse effects such as the formation of neoplasms, remains a significant concern.

The U.S. Food and Drug Administration (FDA) stated:

“Cell-based therapies show great promise for repairing, replacing, restoring, or regenerating damaged cells, tissues and organs. Researchers are working to develop cell-based treatments that are both effective and safe. Many cell-based therapies use stem cells (SC) that are removed from the body and put into cultures in the laboratory, where they multiply before being

infused into the patient. SCs are immature cells that replicate themselves and have the ability to give rise to a variety of different types of cells. For cell therapies based on embryonic stem cells, stem cells are first stimulated to mature before they are given to a patient. However, embryonic stem cells can cause tumors, so products based on them should not have undifferentiated embryonic stem cells contaminating the product given to patients. Also, more mature cells may be better suited for replacing specific types of damaged or lost cells, or for repairing damaged tissue.

A major challenge posed by SC therapy is the need to ensure their efficacy and safety. Cells manufactured in large quantities outside their natural environment in the human body can become ineffective or dangerous and produce significant adverse effects, such as tumors, severe immune reactions, or growth of unwanted tissue. In response to this challenge, FDA scientists are developing laboratory techniques that will enable the agency to carefully evaluate and characterize these products in order to reliably predict whether they will be safe and effective."

REGULATORY STATUS

Concentrated autologous MSCs do not require approval by the U.S. Food and Drug Administration (FDA).

Demineralized bone matrix (DBM), which is processed allograft bone, is considered minimally processed tissue and does not require FDA approval. At least four commercially available DBM products are reported to contain viable stem cells:

- Allostem® (AlloSource) is partially demineralized allograft bone seeded with adipose-derived MSCs
- Allopatch®,
- Osteocell Plus® (NuVasive): an allograft cellular bone matrix containing native MSCs.
- Trinity Evolution Matrix™ (MTF Biologics, gioOrthofix): an allograft that is processed and cryopreserved to maintain viable adult MSCs and osteoprogenitor cells.

Whether these products can be considered minimally manipulated tissue is debated. A product would not meet the criteria for FDA regulation part 1271.10 if it is dependent upon the metabolic activity of living cells for its primary function. Otherwise, a product would be considered a biologic product and would need to demonstrate safety and efficacy for the product's intended use with an investigational new drug and Biologics License Application (BLA).

Other products contain DBM and may be mixed with bone marrow aspirate. Some of the products that are currently available are:

- DBX® Putty (Musculoskeletal Transplant Foundation [MTF]) may be mixed with blood or bone marrow.
- Fusion Flex™ (Wright Medical, part of Stryker): a dehydrated moldable DBM scaffold that will absorb autologous bone marrow aspirate.
- Ignite® (Wright Medical, part of Stryker): an injectable graft with DBM that can be combined with autologous bone marrow aspirate.
- PliaFX® Prime (LifeNet Health) consists of demineralized bone fibers that may be combined with autograft or allograft materials.

Other commercially available products are intended to be mixed with bone marrow aspirate and have received 510(k) clearance, such as:

- CopiOs sponge or paste (Zimmer): synthetic bone graft material consisting of mineralized, lyophilized collagen.
- Collage™ Putty (Orthofix): Composed of type-1 bovine collagen and beta Tri-calcium phosphate.
- Vitoss® (Stryker, developed by Orthovita): composed of beta tricalcium phosphate.
- nanOss® Bioactive (XTant Medical, developed by Pioneer Surgical): nanostructured hydroxyapatite and an open structured engineered collagen carrier.

No products using engineered MSCs have been approved by the FDA for orthopedic applications.

In 2008, the FDA determined that the mesenchymal stem cells sold by Regenerative Sciences for use in the Regenexx™ procedure would be considered drugs or biological products and thus require submission of a New Drug Application (NDA) or Biologics Licensing Application (BLA) to the FDA. In 2014, a federal appellate court upheld FDA's power to regulate adult stem cells as drugs and biologics and ruled that the Regenexx cell product fell within FDA's authority to regulate human cells, tissues, and cellular and tissue-based products (HCT/Ps) (Section 351).[1] To date, no NDA or BLA has been approved by the FDA for this product. As of 2015, the expanded stem cell procedure is only offered in the Cayman Islands. Regenexx™ network facilities in the U.S. provide same-day stem cell and blood platelet procedures, which do not require FDA approval.

EVIDENCE SUMMARY

At this time, the literature consists mainly of articles describing the potential of stem cell therapy for orthopedic applications in humans, along with basic science experiments on sources of mesenchymal stem cells (MSCs), regulation of cell growth and differentiation, and development of scaffolds.[2] Although the evidence base has been steadily increasing, authors indicate that the technology is in an early stage of development. In order to assess the safety and efficacy of orthopedic applications of MSCs and allograft bone products, such as demineralized bone matrix, high-quality randomized trials (RCTs) are required that compare health outcomes with versus without the use of these products.

CARTILAGE DEFECTS

Systematic Reviews

Cao (2025) published a systematic review and meta-analysis of eight RCTs involving 502 participants with unoperated knee osteoarthritis (OA).[3] Five studies used adipose-derived MSCs, and three injected bone marrow derived MSCs. The studies used up to three dose levels. Compared to the control group, MSCs were associated with significantly improved Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores at six and 12 months ($p=0.01$; $p=0.03$ respectively). There was no difference in adverse events ($p>0.05$. Subgroup analysis showed that adipose-derived MSCs were associated with greater improvement than bone marrow derived MSCs. Regarding pain, significant improvement was seen at 6 months ($p=0.0008$) and 12 months ($p=0.0003$) compared to conventional drugs. Heterogeneity was noted to be high at 6 months ($I^2 = 76\%$). Study limitations were noted, including that outcomes were self-reported and subjective, and adverse events were not

consistently reported. The authors concluded that MSCs are safe and are associated with significant improvements in pain and function but additional studies with larger sample sizes are needed to understand optimal cell source and MSC dosage.

Migliorini (2025) published a systematic review of 26 studies that evaluated the management of knee OA using bone marrow aspirate concentrate (BMAC).[4] Ten included studies were RCTs and an additional nine had a prospective study design. Data from 2207 individuals was included. Analysis of two RCTs that compared BMAC to placebo found that BMAC was associated with significant improvement in visual analog scale (VAS) and functional scores up to 11 months. However, the difference was not significant after 12 months. One RCT compared to hyaluronic acid (HA) and found significant improvement in VAS at 12 and 24 months. Other studies compared BMAC to platelet rich plasma and found no difference in functional scores after six months. Meta-analysis could not be performed due to heterogeneity of study designs. The authors conclude that BMAC shows promise, but additional research is needed to assess its effectiveness in managing knee OA.

Carola (2025) published a systematic review of seven studies investigating the use of BMAC in rotator cuff repair surgery.[5] Two of the studies were comparative, and neither showed a difference in patient-reported outcomes (PROMs) between groups. Three of five studies that reported post-operative range of motion (ROM) showed significant improvement in ROM but one comparative study showed no improvement between BMAC and a control group. No complications from BMAC were reported. The authors noted the studies were heterogeneous in terms of study design, patient demographics, surgical techniques, BMAC preparation and application, and outcome measures.

Giorgino (2024) conducted a systematic review evaluating intra-articular MSC injections for the management of hip osteoarthritis (OA).[6] The review included ten studies (N=316) with diverse designs and outcomes, examining pain relief, functional improvement, and cartilage repair through various imaging, pain score, and functional improvement scoring systems and hip outcome score–activities of daily living (HOS-ADL). Results showed favorable outcomes regarding pain relief and functional enhancement, with minimal adverse events (AEs) such as transient joint pain and hematomas. Despite the promising outcomes, the authors highlighted limitations such as small sample sizes, lack of control groups, and heterogeneity in MSC sources and treatment protocols. Further large-scale controlled trials with standardized methodologies are recommended to optimize MSC therapies for hip OA.

Sadeghirad (2024) published a systematic review and meta-analysis of randomized studies to assess the effectiveness of MSC for chronic knee pain due to osteoarthritis (OA). [7] The study involved 16 trials and 807 participants. Thirteen studies used autologous MSC cells and three used allografts. MSC sources were bone-marrow derived in six studies and adipose-derived in eight studies. One study used cells from stromal vascular fraction, and one used placenta-derived cells. At 3-6 months follow-up the analysis found low certainty evidence that MSC injection may reduce pain compared to placebo or conservative management, however high heterogeneity was noted (weighted mean difference [WMD] -2.04 cm on a 10 cm VAS, 95% CI: -2.87 to -1.21; I^2 = 87.2%). At six months, moderate certainty evidence found little to no pain relief (WMD -0.74 cm on a 10cm VAS, 95% CI -1.16 to 1.0.33; I^2 = 0). Similarly at one-year follow-up from six studies (252 participants) there was low certainty evidence of reduced pain (WMD -1.77 cm on a 10 cm VAS, 95% CI: -3.23 to -0.32, I^2 =87%) and moderate certainty evidence reported less pain relief (WMD -.0.73 cm on a 10 cm VAS, 95% CI: -1.69 to 0.24, I^2=49.6%). There was also no evidence of improvement in physical function and some

evidence that MSC therapy may increase risk of any adverse event (risk ration [RR] 2.67, 95% CI 1.19 to 5.99).

Jin (2022) published a systematic review and meta-analysis of 6 RCTs (N=452) that evaluated intra-articular MSC injection in patients undergoing high tibial osteotomy (HTO).[8] Results demonstrated that there were no significant differences in the International Knee Documentation Committee (IKDC) score and KOOS Pain and Symptoms subscales in patients who underwent HTO with or without the MSC injection. However, patients who received MSC injection had significantly greater improvements in Lysholm scores (mean difference, 2.55; 95% CI, 0.70 to 4.40; p=.007), and greater proportions of International Cartilage Regeneration and Joint Preservation Society (ICRS) grade 1 (p=.03) and grade 2 (p=.02) cartilage repair in the medial femoral condyle and grade 2 cartilage repair in the tibial plateau (p=.04).

Rinonpoli (2021) summarized the state of art in the application of stem cells for the treatment of meniscal damage both at pre-clinical and clinical level.[9] Of the 18 studies, 13 were preclinical studies, and 5 were clinical trials. The most commonly used cells were mesenchymal stem cells (MSC), derived from bone marrow (BMMSC), synovial tissue (SMSC), or adipose tissue (ADSC). Follow-ups ranged from 2 to 16 weeks for the pre-clinical studies and from 3 to 24 months for the clinical studies. All studies documented good results in terms of laboratory markers/scores, clinical and radiologic evaluation. The authors concluded that based on the currently available data, it is not possible to establish the best cell source or delivery method for the treatment of meniscal injuries.

Wiggers (2021) conducted a systematic review of RCTs evaluating autologous MSC therapy on patient-reported outcome measures and disease severity.[10] Fourteen RCTs were identified in searches conducted through December 2020. Meta-analysis was precluded because most of the original trial data were not available for pooling and due to heterogeneity across studies. A total of 408 patients with knee osteoarthritis received MSC therapy derived from bone marrow, adipose tissue or activated peripheral blood. After 1 year, 19 of 26 (73%) clinical outcome measures improved with MSCs compared with control. In the MSC group, patients improved by 1.8 to 4.4 points on the Visual Analogue Scale (0 to 10) and 18 to 32 points of the Knee Osteoarthritis Outcome Score (0 to 100). Four studies showed better disease severity on imaging after MSC compared with control at 1 year. Although the reviewers found a positive effect of autologous MSC therapy compared with control treatments, the certainty of the evidence was rated low to very low due to high risk of bias in the included studies (e.g., 10 of 14 RCTs were at high risk of bias on all outcomes) and high heterogeneity in the source, method of preparation, and dosage of injected stem cells in included RCTs.

A systematic review and meta-analysis by Maheshwer (2020) identified 25 studies with 439 participants that used MSCs for treatment of OA.[11] Although 13 studies were considered level I RCTs by the authors (range of 7 to 40 participants), low quality RCTs would normally be downgraded to level II. Meta-analysis suggested improvement in self-reported function, but only in patients who underwent concomitant surgery, and there was no significant improvement in pain. Few studies reported on cartilage quality. Most of the studies were rated as poor or fair quality. Conclusions are limited due to substantial variability in MSC source, preparation, and concentration in the current literature.

A systematic review by Borakati (2018) included 13 studies comparing patients with osteoarthritis who were treated either with MSCs or with a control treatment that was identical other than the inclusion of MSCs (i.e., studies using chondrogenic cellular therapy as a control

were not included).[12] Pain assessment results were noted for each of the controlled studies, resulting in a pooled standardized mean difference (SMD) of -1.27 (95% confidence interval [CI] -1.95 to -0.58) in favor of the group treated with MSCs. Reviewers reported a Z-statistic effect size of 3.62, again in favor of the groups treated with MSCs ($p<0.001$); although they noted the high heterogeneity across controlled studies ($I^2=92\%$). Additionally, 34 uncontrolled studies (n=737 patients) were summarized and evaluated qualitatively: reviewers noted consistent cartilage regrowth and reduction of pain following treatment with MSCs in these studies; however, as pain medication was often given concurrently, interpretation of the latter outcome is limited.

Emadedin (2018) reported a triple-blind placebo-controlled phase 1/2 trial of expanded MSCs in 47 patients with OA of the knee.[13] Compared to the placebo group, the MSC group showed statistically significant improvements in WOMAC pain and function subscales but not VAS. The WOMAC stiffness subscale improved to a similar extent in the two groups. Minimum Clinically Important Improvement and Patient Acceptable Symptom State were not significantly different between the two groups. Study limitations included the short duration of follow-up, statistical analysis, and lack of information regarding use of analgesic medications.

Iijima (2018) published a systematic review of MSC treatment for knee osteoarthritis, which included 35 studies.[14] Of these, only seven were RCTs. Meta-analysis results indicated that there was improvement in knee pain (SMD -1.45, 95% CI -1.94 to -0.96), cartilage quality (SMD -1.99, 95% CI -3.51 to -0.47), and self-reported function (SMD 1.50, 95% CI 1.09 to 1.92), however the authors stated that the evidence quality was “very low” to “low,” and emphasized the need for high-quality RCTs.

Another 2018 systematic review on stem cell therapy for articular cartilage repair noted similar concerns regarding the quality of the evidence.[15] The review included 46 studies that evaluated MSCs from a variety of sources, most of which were case reports and case series. The authors noted that among these, “18 studies erroneously referred to adipose tissue-derived stromal vascular fractions as "adipose-derived MSCs," 2 studies referred to peripheral blood-derived progenitor cells as "peripheral blood-derived MSCs," and 1 study referred to bone marrow aspirate concentrate as "bone marrow-derived MSCs."

Cui (2016) published a systematic review on 18 studies looking at the effect of MSC in treating patients with osteoarthritis.[16] MSC treatment in patients with KOA showed continual efficacy for 24 months compared with their pretreatment condition. Effectiveness of MSCs was improved at 12 and 24 months post-treatment, compared with at three and six months. There was no dose response association in the MSCs numbers. This review only included four randomized trials while the remaining 14 studies were non-randomized and had methodological limitations.

Xu (2015) published a meta-analysis on the effect of MSCs for articular cartilage degeneration treatment, including 11 controlled trials (n=558). No critical appraisal of the quality of the included studies was reported. MSC treatment significantly improved the American Orthopedic Foot and Ankle Society Scale (SMD 0.91, 95% confidence interval [CI], 0.52 to 1.29) and the Osteo-Arthritis Outcome Score (SMD 2.81, 95% CI 2.02 to 3.60).[17] Comprehensive evaluation indexes, such as the American Knee Society Knee Score System (SMD -0.12, 95% CI -1.02 to 0.78), the Hospital for Special Surgery Knee Rating Scale (SMD 0.24, 95% CI -0.56 to 1.05) and the International Knee Documentation Committee (SMD -0.21, 95% CI -0.77 to 0.34), were no different between MSC use and other treatments. The reviewers concluded that there

was no obvious advantage regarding the application of stem cells to treat cartilage injury, compared with other treatments.

Filardo (2013) conducted a systematic review of mesenchymal stem cells for the treatment of cartilage lesions.[18] They identified 72 preclinical papers and 18 clinical reports. Of the 18 clinical reports, none were randomized, five were comparative, six were case series, and seven were case reports. In two clinical studies the source of MSCs was adipose tissue, in five it was bone marrow concentrate, and in 11 studies the source of MSCs was bone marrow-derived. The authors reached the following conclusion:

> "Despite the growing interest in this biological approach for cartilage regeneration, knowledge on this topic is still preliminary, as shown by the prevalence of preclinical studies and the presence of low-quality clinical studies. Many aspects have to be optimized, and randomized controlled trials are needed to support the potential of this biological treatment for cartilage repair and to evaluate advantages and disadvantages with respect to the available treatments."

The source of MSCs may have an impact on outcomes, but this is not well understood, and the available literature uses multiple different sources of MSC. Because of the uncertainty over whether these products are equivalent, the summary of the key evidence to date is grouped by source of MSC.

Randomized Controlled Trials

Cartilage Defects: MSCs Expanded from Bone Marrow

Pers (2024) published results of the RESPINE study of allogeneic bone marrow-derived MSC therapy for individuals with chronic low back pain.[19] RESPINE was a prospective double-blind RCT that compared MSC to sham treatment in 114 participants. Co-primary endpoints were improvement of pain using the Visual Analog Scale (VAS) by 20% or improvement in disability according to the Oswestry Disability Index (ODI) by 20%, and disc fluid content between baseline and month 12. The primary endpoint was not reached (74% treatment vs 69% control; p=0.77). There were no serious adverse events reported. The authors concluded that while the efficacy of MSC therapy for chronic low back pain was not demonstrated, the treatment is safe.

Mautner (2023) compared multiple autologous and allogeneic cell-based therapies with gold-standard corticosteroid injection in 475 adults with OA of the knee in a single-blind phase 3 RCT.[20] Patients were randomized to one of two autologous cell therapies (bone marrow aspirate concentrate [BMAC] or stromal vascular fraction), allogeneic umbilical cord-derived MSCs, or intra-articular corticosteroid injection; the co-primary endpoints were changes from baseline in VAS and Knee injury and Osteoarthritis Outcome Score pain scores at 12-month follow-up. No significant differences in pain scores were noted in comparisons between corticosteroid injection and any of the cell therapy arms. The authors concluded that the study found no superiority of any of the cell therapies compared to corticosteroids at one year.

Wong (2013) reported on the use of cultured MSCs in 56 patients with osteoarthritis who underwent medial opening-wedge high tibial osteotomy and microfracture of a cartilage lesion.[21] Bone marrow was harvested at the time of microfracture and the MSCs were isolated and cultured. After three weeks, the cells were assessed for viability and delivered to the clinic, where patients received an intra-articular injection of MSCs suspended in hyaluronic acid (HA) or, for controls, intra-articular injection of HA alone. The primary outcome was the International

Knee Documentation Committee (IKDC) score at six months, one year, and two years. Secondary outcomes were the Tegner and Lysholm scores through two years and the Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART) scoring system by MRI at one year. All patients completed the two-year follow-up. After adjusting for age, baseline scores, and time of evaluation, the group treated with MSCs showed significantly better scores on the IKDC (mean difference 7.65 on 0 to 100 scale, p=0.001), Lysholm (mean difference, 7.61 on 0 to 100 scale, p=0.02), and Tegner (mean difference 0.64 on a 0 to 10 scale, p=0.02). Blinded analysis of MRI results found higher MOCART scores in the MSC group. The group treated with MSCs had a higher proportion of patients who had complete cartilage coverage of their lesions (32% vs 0%), greater than 50% cartilage cover (36% vs 14%) and complete integration of the regenerated cartilage (61% vs 14%).

A controlled, double-blind clinical trial was conducted with a group of 47 patients with radiographic and symptomatic knee osteoarthritis.[22] Three groups were randomized for intra-articular injections: autologous bone marrow-derived culture-expanded MSCs (n=16); autologous bone marrow-derived culture-expanded MSCs with platelet-rich plasma (PRP) (n=14); and corticosteroid (n=17). The results of the study show Knee Injury and Osteoarthritis Outcome Score (KOOS) is significantly improved at one month (p=0.003) with MSCs and by one year both MSCs and MSCS + PRP show the highest percentage of improvement.

Cartilage Defects: MSCs Concentrated from Bone Marrow

A small RCT published by Vega (2015) that assessed the efficacy of bone marrow derived MSCs as a treatment for knee osteoarthritis, randomizing 30 patients with chronic knee pain unresponsive to conservative treatments and showing radiological evidence of osteoarthritis.[23] Fifteen patients were treated with allogeneic bone marrow MSCs by intra-articular injection, while 15 controls received intra-articular hyaluronic acid (HA). Clinical outcomes were followed for one year and included evaluations of pain, disability, and quality of life. Articular cartilage quality was assessed by quantitative magnetic resonance imaging T2 mapping. The MSC-treated patients displayed significant improvement in algofunctional indices versus the active controls. Quantification of cartilage quality by T2 relaxation measurements showed a significant decrease in poor cartilage areas, with cartilage quality improvements in MSC-treated patients.

Cartilage Defects: Adipose-Derived MSCs

Kim (2023) reported a double-blind phase 3 RCT comparing a single intra-articular injection of autologous adipose tissue-derived MSCs with placebo in patients with knee OA (N=261).[24] Patients meeting American College of Rheumatology criteria for Kellgren-Lawrence grade 3 knee OA who had 100 mm VAS pain scores ≥50 and WOMAC functional impairment scores ≥40 despite >3 months of non-operative treatment were eligible for enrollment. All patients underwent abdominal subcutaneous lipoaspiration three weeks prior to assigned study injection (1:1 randomization to 1x108 autologous adipose tissue-derived MSCs [n=131] or a mixture of saline with autologous serum [n=130]). The co-primary endpoints were change in 100 mm VAS pain score and WOMAC function score from baseline to 6 months. In the primary analysis, patients assigned to adipose tissue-derived MSCs experienced significantly greater improvements than those assigned to placebo in both VAS pain score (25.2 ±24.6 vs 15.5 ±23.7; p=.004) and WOMAC function score (21.7 ±18.6 vs 14.3 ±19.2; p=.002) from baseline to 6 months. Six-month changes in patient-reported outcomes (KOOS, 36-Item Short Form Health Survey Score, and International Knee Documentation Committee subjective knee

score) also reflected significant improvements in patients who received adipose tissue-derived MSCs compared with those who received placebo. Study limitations include that while patients were required to have received prior non-operative therapy for at least 3 months, specific prior treatments were not reported; it is unclear whether the use of a placebo comparator was more appropriate than an active comparator in this setting.

The literature on adipose-derived MSCs for articular cartilage repair is very limited, coming from two research groups in Korea. One of the groups appears to have been providing this treatment as an option for patients for a number of years and recently published a RCT that evaluated cartilage healing after high tibial osteotomy (HTO) in 52 patients with osteoarthritis of the medial compartment.[25] Patients were randomly assigned to HTO with application of platelet-rich plasma (PRP) or HTO with application of PRP plus MSCs. MSCs from adipose tissue were obtained through liposuction from the buttocks. The tissue was centrifuged and the stromal vascular fraction mixed with PRP for injection. A total of 44 patients completed second look arthroscopy and one- and two-year clinical follow-up. There were statistically significant differences for PRP only versus PRP+MSC on the Knee Injury and Osteoarthritis Outcome Score (KOOS) subscales for pain (74±5.7 vs. 81.2±6.9, p<0.001) and symptoms (75.4±8.5 vs. 82.8±7.2, p=0.006). There were also statistically significant differences on the final pain score for the PRP only versus PRP+MSC groups (16.2±4.6 vs. 10.2±5.7, p<0.001), but the Lysholm score, which is more scientifically proven, was not significantly different between the PRP only and PRP+MSC groups (80.6±13.5 vs. 84.7±16.2, all respectively, p=0.36). Articular cartilage healing was rated as improved with MSCs following video review of second-look arthroscopy; blinding of this measure is unclear. There are a number of limitations of this study, including the small sample size, short duration of follow-up, and significant improvements on only some of the outcomes. All of the significant differences in outcomes were modest in magnitude, and as a result, there is uncertainty regarding the clinical significance of the findings.

This group also published a trial comparing treatment with adipose-derived MSCs, fibrin glue, and microfracture to microfracture alone.[26] A total of 80 patients with a single International Cartilage Repair Society grade III/IV symptomatic cartilage defect on the femoral condyle were randomized to receive one of the treatments. The mean follow-up time was 27.4 months. At follow-up, the MSC + fibrin glue + microfracture group had significantly greater improvements in the Knee Injury and Osteoarthritis Outcome Score pain and symptom subscores than the microfracture alone group (p=0.034 and 0.005, respectively). There were no significant differences between groups for the activities of daily living, sports and recreation, or quality of live subscores. Second-look arthroscopies were performed in 57 of the 80 patients, with no significant differences between groups. The lack of blinding in this study limits the conclusions that can be drawn from its results.

More recently, Zaffagnini (2022) reported on results of an RCT that evaluated a single intra-articular injection of microfragmented adipose tissue or PRP in patients (N=118) with knee OA.[27] The primary outcomes were the IKDC subjective score and the KOOS pain subscore at 6 months. Overall, both treatments provided significant improvements from baseline in clinical outcomes, with no significant differences found between treatment groups. The IKDC scores significantly improved from baseline to 6 months, from 41.1 ± 16.3 to 57.3 ± 18.8 with microfragmented adipose tissue, and from 44.8 ± 17.3 to 58.4 ± 18.1 with PRP. The improvement in the KOOS pain subscore from baseline to 6 months was 58.4 ± 15.9 to 75.8 ± 17.4 with microfragmented adipose tissue and 63.5 ± 17.8 to 75.5 ± 16.1 with PRP. As a secondary outcome, more patients in the microfragmented adipose tissue group with

moderate/severe knee OA reached the minimal clinically important difference for the IKDC score at 6 months compared with the PRP group (75.0% vs 34.6%, respectively; p=.005).

A multisite prospective double-blinded randomized placebo-controlled clinical trial was conducted in adult patients with symptomatic knee osteoarthritis.[28] The trial included 39 eligible patients injected with high-dose, low-dose, or placebo stromal vascular fraction medium obtained from liposuction for intra-articular administration of progenitor cells and mesenchymal stem cells derived from adipose tissue. After six months, change in WOMAC score was 83.9%, 51.5%, and 25.0%, respectively, and at one year was 89.5%, 68.2%, and 0%, respectively. Significant changes when compared with placebo revealed a dose dependent improvement in osteoarthritis symptoms and pain at six months (high dose, p=0.04; low does, p=0.02) and at one year (high dose, p=0.006; low dose, p=0.009).

Cartilage Defects: MSCs from Peripheral Blood

A 2013 report described a small randomized controlled trial with autologous peripheral blood MSCs for focal articular cartilage lesions.[29] Fifty patients with grade 3 and 4 lesions of the knee joint underwent arthroscopic subchondral drilling followed by five weekly injections of HA. Half of the patients were randomly allocated to receive injections of peripheral blood stem cells or no further treatment. There were baseline differences in age between the groups, with a mean age of 38 for the treatment group compared to 42 for the control group. The peripheral blood stem cells were harvested after stimulation with recombinant human granulocyte colony-stimulating factor, divided in vials, and cryopreserved. At six months after surgery, HA and MSC were re-administered over three weekly injections. At 18 months after surgery, second look arthroscopy on 16 patients in each group showed significantly (p=.022) higher histological scores (by about 10%) for the MSC group (1,066 vs. 957 by independent observers) while blinded evaluation of MRI showed a statistically significant (p=0.013) higher morphologic score (9.9 vs. 8.5). There was no difference in International Knee Documentation Committee (IKDC) scores between the two groups at 24 months after surgery. It is uncertain how differences in patient age at baseline may have affected the response to subchondral drilling.

Cartilage Defects: MSCs from Synovial Tissue

Akgun (2015) reported a small (n=14) investigator-blinded RCT that compared matrix-induced autologous MSCs from synovial tissue versus matrix-induced autologous chondrocyte implantation (MACI).[30] Both chondrocytes from cartilage and MSCs from synovia were harvested in an arthroscopic procedure, expanded in culture, and then cultured on a collagen membrane for two days. Implantation was performed with the cells facing the subchondral bone. Follow up evaluations were made through 24 months post-procedure. Outcomes on the KOOS subscales and the VAS pain score were statistically better in the MSC group than the MACI group ($p<0.05$) at the six-month follow up, although it is not clear if the difference observed would be considered clinically significant. Studies with larger samples sizes and follow-up supported by histological analyses are necessary to determine long-term outcomes of this treatment.

Cartilage Defects: MSCs from Umbilical Cord Blood

Lim (2021) reported on a RCT of 114 patients with large, full-thickness cartilage defects (International Cartilage Repair Society grade 4) treated with either a composite of umbilical cord-derived MSCs plus 4% hyaluronate (MSC-HA) or microfracture.[31] The study consisted of a 48-week phase 3 clinical trial and a 5-year follow-up study (64%). Of 114 patients

randomized, 89 completed the phase 3 trial (78.1%) and 73 were enrolled in the follow-up study (64.0%). The primary outcome, proportion of participants with cartilage restoration equivalent to at least 1 grade improvement on the ICRS Macroscopic Cartilage Repair Assessment at 48-week arthroscopic evaluation, was 97.7% (42/43) in the MSC-HA group and 71.7% (33/46) in the microfracture group (odds ratio, 16.55; 95% CI, 2.06 to 133.03; P =.001). Both groups had significantly improved patient-reported pain scores (VAS pain, WOMAC, and IKDC scores) at 48 weeks versus baseline, but there was no significant difference between the 2 groups at this timepoint. From 36 to 60 months after intervention, the significant improvements from baseline were maintained in the MSC-HA group, whereas the improvements in VAS pain and WOMAC deteriorated in the microfracture group. This study had several limitations. There was no intervention group that received MSC alone, the comparator (microfracture) is not considered the standard of care for large, full-thickness cartilage defects, surgeons and participants were not blinded to treatment outcome, and there was high loss to follow-up. These limitations, along with a lack of improvement in patient-reported outcomes in the intervention group at 48 weeks, preclude drawing conclusions about the effectiveness of umbilical cord blood-derived MSCs in this population; higher quality evidence from RCTs is needed.

Section Summary

The evidence base on MSCs for cartilage repair is increasing, although nearly all studies to date have reported a variety of methods of MSC preparation. Some randomized studies have reported improvements in histologic, morphologic and functional outcomes, but others have found MSCs are not superior to standard treatment. Meta-analyses have found reduction of pain in groups treated with MSCs, although high heterogeneity is noted. Long-term efficacy has not been established. Studies did not consistently distinguish between improvements due to MSCs and those due to pain medication. The method of preparation used in one positive study was to obtain MSCs from bone marrow at the time of microfracture, culture (expand) over a period of three weeks, and then inject into the knee in a carrier of HA. Another randomized trial, using MSCs from peripheral blood, found improvements in histologic and morphologic outcomes, but not functional outcomes, following stimulation with recombinant human granulocyte colony-stimulating factor. A third small RCT found that MSCs from synovial tissue and cultured in collagen resulted in outcomes at least as good as those following MACI.

FUSION AND NON-UNION

There is limited evidence on the use of allografts with stem cells for fusion of the extremities or spine or for the treatment of non-union. No RCTs for this indication were identified.

Eastlack (2014) reported outcomes from a series of 182 patients who were treated with anterior cervical discectomy and fusion using Osteocel Plus in a PEEK cage and anterior plating.[32] At 24 months, 74% of patients (180/249 levels treated) were available for follow-up. These patients had significant improvements in clinical outcomes; 87% of levels achieved solid bridging and 92% of levels had range of motion less than 3º. With 26% loss to follow-up at 24 months and lack of a standard of care control group, interpretation of these results is limited.

One retrospective series from 2009 was identified on the use of Trinity MSC bone allograft for revision surgery of the foot and ankle.[33] Twenty-three patients were included who had undergone revision foot and/or ankle surgery for residual malunion, non-union, or significant segmental bone loss. Patients were followed to the point of radiographic and clinical union, which occurred at a median of 72.5 days for 21 of the 23 patients (91.3%). However, these

outcomes do not permit conclusions because of a lack of a control group for comparison with patients who received stem-cell therapy.

Section Summary

Current evidence is insufficient to determine whether the use of stem cell results in superior outcomes such as higher fusion rates, or lower rates of reoperations and adverse events.

MENISCECTOMY

Vangsness (2014) reported an industry-sponsored phase 1/2 randomized, double-blind, multicenter study of cultured allogeneic MSCs (Chondrogen™, Osiris Therapeutics) injected into the knee after partial meniscectomy.[34] The 55 patients were randomized to intra-articular injection of either 50´106 allogeneic MSCs, 150´106 allogeneic MSCs in HA, or HA vehicle control at 7 to 10 days after meniscectomy. The cultured MSCs were derived from bone-marrow aspirates from unrelated donors. At two-year follow-up, three patients in the low-dose MSC group had significantly increased meniscal volume measured by MRI (with an a priori determined threshold of at least 15%) compared to none in the control group and none in the high-dose MSC group. There was no significant difference between the groups in the Lysholm Knee Scale. On subgroup analysis, patients with osteoarthritis who received MSCs had a significantly greater reduction in pain at two years compared with patients who received HA alone. This appears to be a post hoc analysis and should be considered preliminary. No serious adverse events were thought to be related to the investigational treatment.

Section Summary

Current evidence for the use of stem cells as an adjunct to meniscectomy is limited to a single preliminary RCT. The outcomes of this study must be validated in large, long-term, randomized controlled trials.

OSTEONECROSIS

Several randomized comparative trials have been identified that evaluated the use of MSCs for osteonecrosis of the femoral head.

Osteonecrosis: MSCs Expanded from Bone Marrow

Zhao (2012) reported a randomized trial that included 100 patients (104 hips) with early stage femoral head osteonecrosis treated with core decompression and expanded bone marrow MSCs versus core decompression (CD) alone.[35] At 60 months after surgery, two of the 53 hips (3.7%) treated with MSCs continued to have progressive disease and underwent vascularized bone grafting, compared with 10 of 44 hips (23%) in the decompression group who had disease progression and underwent either vascularized bone grafting (n=5) or total hip replacement (n=5). In addition, treatment with MSC improved Harris Hip scores compared to CD and decreased the volume of the necrotic lesion of the hips preoperatively classified at stage IC, IIB, and IIC ($p<0.05$, respectively; stage IIA, $P=0.06$, respectively).

Osteonecrosis: MSCs Concentrated from Bone Marrow

A 2017 randomized, double-blind trial was conducted using autologous bone marrow concentrate in 38 patients with stage three osteonecrosis.[36] A control group of core decompression plus saline injection was compared to patients receiving core decompression

plus MSC implantation. The primary outcome was needing total hip replacement and secondary outcomes were clinical symptoms such as pain and functional ability. There was no difference between groups on any outcomes including total hip replacement requirements, clinical tests, or radiologic evidence.

Another small trial randomized 40 patients (51 hips) with early stage femoral head osteonecrosis to core decompression plus concentrated bone marrow MSCs or core decompression alone.[37] Blinding of assessments in this small trial was not described. Harris Hip Score (HHS) was significantly improved in the MSC group (scores of 83.65 and 82.42; $p<0.05$) compared with core decompression (scores of 76.68 and 77.39). Kaplan-Meier analysis showed improved hip survival in the MSC group (mean of 51.9 weeks) compared with the core decompression group (mean of 46.7 weeks). There were no significant differences between the groups in the radiographic assessment or MRI results. The conflicting report of improvement via HHS compared to no observable improvement via MRI, may point to the need for study blinding to control for confounding bias toward treatment.

Section Summary

Two small studies reported improvement in the Harris Hip Score in patients with osteonecrosis of the femoral head treated with core decompression and MSCs, although it was not reported if the patients or investigators were blinded to the treatment group. Hip survival was significantly improved following treatment with either expanded or concentrated MSCs. The effect appears to be larger with expanded MSCs compared with concentrated MSCs.However, a double-blind RCT found no difference between MSC treatment or saline injection, when combined with core decompression. Additional studies with a larger number of patients are needed to permit greater certainty regarding the effect of this treatment on health outcomes.

BONE FRACTURES

A systematic review by Yi (2022) explores the application potential of MSCs for healing bone fractures.[38] Of the 31 articles, 26 were preclinical studies (n = 913), and 5 were clinical trials (n = 335). Preclinically, MSCs therapy significantly augmented the progress of bone regeneration [(bone volume over tissue volume (MD7.35, $p < 0.01$)], despite some non-significant effects (on the callus index, bone strength, work to failure, and stiffness). Clinically, the MSC group had a significantly reduced incidence of poor recovery (odds ratio (OR) 0.30, $p < 0.01$); however, a significant decrease in healing time was not observed in the MSC group (MD 2.47, $p = 0.26$). The authors suggest that the patients have benefited from MSC administration but larger RCTs are needed to confirm these findings.

Section Summary

Current evidence for the use of stem cells for healing bone fractures is limited to a single systematic review. Larger RCTs are required to confirm the clinical and preclinical findings.

PRACTICE GUIDELINE SUMMARY

American College of Rheumatology and Arthritis Foundation

In 2019, guidelines from the American College of Rheumatology and Arthritis Foundation on osteoarthritis (OA) of the hand, hip, and knee gave a strong recommendation against stem cell injections in patients with knee and/or hip OA, noting the heterogeneity in preparations and lack of standardization of techniques.[39] No recommendation was made for hand OA, since

efficacy of stem cells has not been evaluated.

American Academy of Orthopaedic Surgeons

A 2022 guideline from the American Association of Orthopaedic Surgeons on surgical management of osteoarthritis of the knee does not address the use of stem cell therapy.[40] The guideline is endorsed by Arthroscopy Association of North American (AANA) and the American Association of Hip and Knee Surgeons.

A 2020 guideline from American Association of Orthopaedic Surgeons on the management of glenohumeral joint OA, endorsed by several other societies, states that injectable biologics such as stem cells cannot be recommended in the treatment glenohumeral joint OA.[41] There was consensus from the panel that better standardization and high-quality evidence from clinical trials is needed to provide definitive evidence on the efficacy of biologics in glenohumeral OA. The strength of evidence was rated as no reliable scientific evidence to determine benefits and harms. The 2013 guideline on treatment of osteoarthritis of the knee does not address stem cell injections.

American Association of Neurological Surgeons

In 2014, the American Association of Neurological Surgeons guidelines on fusion procedures for degenerative disease of the lumbar spine relevant to this evidence review have indicated that “The use of demineralized bone matrix (DBM) as a bone graft extender is an option for 1- and 2-level instrumented posterolateral fusions. Demineralized Bone Matrix: Grade C (poor level of evidence).”[42]

SUMMARY

There is not enough research to know if or how well mesenchymal stem cells (MSCs), allograft bone products containing stem cells, or synthetic bone graft substitutes that must be combined with autologous bone marrow work to treat people with orthopedic conditions. No clinical guidelines based on research recommend MSC treatment, allograft bone products containing stem cells, or synthetic bone graft substitutes that must be combined with autologous bone marrow for people with orthopedic conditions. Therefore, use of stem cells for orthopedic applications is considered investigational.

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CODES

NOTE: There are no specific codes for orthopedic applications of stem cell therapy. The appropriate CPT code for reporting this procedure is 20999, or the code for an unlisted procedure of the body area on which the procedure is performed.

Codes	Number	Description
CPT	0565T	Autologous cellular implant derived from adipose tissue for the treatment of osteoarthritis of the knees; tissue harvesting and cellular implant creation
	0566T	Injection of cellular implant into knee joint using ultrasound guidance, unilateral
	0717T	Autologous adipose-derived regenerative cell (ADRC) therapy for partial thickness rotator cuff tear; adipose tissue harvesting, isolation and preparation of harvested cells, including incubation with cell dissociation enzymes, filtration, washing and concentration of ADRCs
	0718T	Autologous adipose-derived regenerative cell (ADRC) therapy for partial thickness rotator cuff tear; injection into supraspinatus tendon including ultrasound guidance, unilateral
	0737T	Xenograft implantation into the articular surface
	1092T	Implantation of acellular scaffold (eg, hyaluronan), knee, single implant; into chondral defect, open
	1093T	Implantation of acellular scaffold (eg, hyaluronan), knee, single implant; into a chondral or osteochondral defect, arthroscopic
	1094T	Implantation of acellular scaffold (eg, hyaluronan), knee, single implant; each additional acellular scaffold implantation (List separately in addition to code for primary procedure)
	1095T	Harvesting and processing of autologous bone marrow aspirate concentrate (BMAC), with application onto scaffold or injection into anatomical recipient site (eg, subchondral bone, joint space, chondral lesion), including imaging guidance, when performed, for therapeutic musculoskeletal treatment, excluding spinal procedures
	20939	Bone marrow aspiration for bone grafting, spine surgery only, through separate skin or fascial incision (List separately in addition to code for primary procedure)
	20999	Unlisted procedure, musculoskeletal system, general
	21899	Unlisted procedure, neck or thorax
	22899	Unlisted procedure, spine
	23929	Unlisted procedure, shoulder
	24999	Unlisted procedure, humerus or elbow
	25999	Unlisted procedure, forearm or wrist
	26989	Unlisted procedure, hands or fingers
	27299	Unlisted procedure, pelvis or hip joint
	27599	Unlisted procedure, femur or knee
	27899	Unlisted procedure, leg or ankle
	28899	Unlisted procedure, foot or toes
	29999	Unlisted procedure, arthroscopy
	38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
	38230	Bone marrow harvesting for transplantation; allogeneic
	38232	Bone marrow harvesting for transplantation; autologous
	38241	Bone Marrow or blood-derived peripheral stem cell transplantation; autologous
HCPCS	None	

Date of Origin: *September 2011*