2024

Minimally Invasive Therapies in the Treatment of Arthropathy

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by

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Bachelor of Science, North Dakota State University, 2018

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A Scholarly Project

Submitted to the Graduate Faculty of the University of North Dakota

in partial fulfillment of the requirements for the degree of

Master of Physician Assistant Studies

Grand Forks, North Dakota

May 2024

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Acknowledgments

I would like to thank my advisor, Jay Metzger, Professor Vicki Andvik, and librarian Megan Denis for their efforts in support of this project. I would additionally like to thank the broader faculty of the University of North Dakota's Department of Physician Assistant Studies for their abundance of patience and grace with this academic hurdle. My thanks also to the friends and family who have lent their aid throughout this challenging period of training and education.

Abstract

It is estimated that 27% of adults over 45 years of age suffer from osteoarthritis of the hip secondary to articular cartilage damage over the lifespan. Joint pain diminishes life quality, limits range of motion and overall activity, and frequently impairs basic ambulation. These functional deficits worsen the progression of comorbidities that are often referred to as lifestyle-related chronic disease as physical activity subsequently declines. This literature review explores the efficacy of minimally invasive therapies that precede and delay surgical intervention in adult patients experiencing functional limitations and pain in major joints. The study examines the effectiveness of various interventions, including physical therapy, corticosteroid injection, hyaluronic acid injection, platelet-rich plasma injection, and mesenchymal stem cell (MSC) injection. A comprehensive search of PubMed utilizing MeSH terms yielded 114 relevant studies, which were screened based on inclusion criteria. Keywords such as "mesenchymal stem cells," "arthroplasty," and "joints" were used in the search process. While the review reveals a limited number of studies on MSC therapies with small sample sizes, their proposed mechanism of action remains promising. Low side-effect profiles and evidence of induced regeneration within the joints are encouraging, but studies evaluating their effectiveness compared to other treatments are lacking. Incidentally, findings suggest that corticosteroid injections may accelerate joint disease progression, underscoring the value of alternative treatments such as hyaluronic acid or platelet-rich plasma in the early stages of arthropathy. In conclusion, although MSC therapies lack a robust evidence base, their potential warrants further investigation, while caution is advised regarding the use of corticosteroids in the management of arthropathy.

Key Words: Arthropathy, Mesenchymal Stem Cells, Regenerative Medicine

Introduction

It is estimated that 27% of adults over 45 years of age suffer from osteoarthritis of the hip secondary to articular cartilage damage over the lifespan. This figure swells to 42% once adults reach age 75 (Urits, 2020), with over 12% of these total cases secondary to traumatic injury (Phen & Shenker, 2019). Joint pain diminishes life quality, limits range of motion and overall activity, and frequently impairs basic ambulation. These functional deficits worsen the progression of comorbidities that are often referred to as lifestyle-related chronic disease (examples such as diabetes, cardiovascular disease, obesity, and impaired sleep) as physical activity subsequently declines. Treatments for arthropathies of many kinds rely on a spectrum of conservative to more invasive interventions, beginning typically with physical therapy, nonsteroidal anti-inflammatory drugs (NSAIDs) with analgesics, intra-articular (IA) treatments, and arthroplasty (in order). This literature review aims to consider the efficacy of contemporary, less invasive treatments against that of novel biologics such as mesenchymal stem cell therapy.

Statement of the Problem

Access to definitive treatment for adults residing in rural areas suffering from pain or functional deficits in major joints is limited. Contemporary treatments focus on the restoration of function, range of motion, and reduction of pain through a spectrum of conservative management techniques ranging from physical therapy to intra-articular injection. Stem cell application may augment conservative therapies, directly address underlying pathology, or delay the need for surgical intervention in syndromes of intra-articular damage to ligament, tendon, or cartilage of these joints or their adjacent structures. While arthroplastic intervention predominates definitive treatments today, regenerative medicine technologies may provide less invasive relief in the near future.

Research Question

Does the use of mesenchymal stem cell therapies restore tissue integrity, functional utility, or significantly delay surgical intervention of major joints compared to conservative and minimally invasive alternatives in adult patients with functional deficit or pain in any major joints that involves damage to tendon, ligament, cartilage, or arthritic changes?

Methods

MeSH term search of PubMed yielded 114 results. Titles and abstracts reviewed for relevance. Initial inclusion criteria began constrained to human studies within five years from publication, later expanded to 10 years from publication. Keywords included: mesenchymal stem cells, arthroplasty, and joints. Similar articles, cited by articles, and reference articles within studies and in the literature review results were considered for inclusion.

Literature Review

As stated by Urits et al. (2020), 27% of adults over 45 suffer from osteoarthritis (OA) of the hip secondary to articular cartilage damage over the lifespan. This figure swells to 42% once adults reach age 75. While their focus was OA-related, joint pain sufferers as a whole experience diminished life quality, which frequently includes limitations in ambulation and range of motion. These functional impairments worsen the progression of what are sometimes referred to as lifestyle-related chronic diseases (comorbidities such as diabetes, cardiovascular disease, obesity, and impaired sleep) as physical activity declines.

Approximately 12% of all patients with osteoarthritis of the hip, knee, or ankle suffer secondarily to post-traumatic osteoarthritis (PTOA). The incidence of PTOA remains steady despite improvements in therapies. PTOA predominantly affects younger patients who are poor candidates for arthroplasty, given the limited life span of implants. Given its structure, hyaline

(articular) cartilage is inherently limited in regeneration. Injury reduces RNA expression of collagen, promotes internucleosomal DNA fragmentation, and results in a surge of proinflammatory cytokines, events that result in subchondral damage, increased bone resorption, and promotion of the collapse of the articular surface (Phen & Shenker, 2019).

Current pharmacologic therapies address established osteoarthritis, attenuating inflammation and its toxicity towards chondrocytes to preserve articular integrity. Glucocorticoids (GC) are commonly used but are associated with gross cartilage damage and chondrotoxicity at higher concentrations (Phen & Shenker, 2019). Recent animal studies suggest the promotion of chondrocyte viability if GC are administered following injury, but these are still early results with uncertain benefits in humans (Heard, 2015). Bisphosphonates have been shown to reduce cartilage degeneration acutely. However, degeneration was seen uniformly in the weeks that followed. Hyaluronan (HA) supplementation is another popular treatment in established osteoarthritis, reducing osteochondral defects in rodents (Galois, 2012), but canine models compared to placebo showed little improvement outside of increased activity levels secondary to what is hypothesized to be analgesic effect (Smith, 2001).

Currently, mesenchymal stem cells (MSC) are most often utilized as surgical adjuncts, but emerging studies have begun to evaluate isolated treatment by MSCs. While chondrogenesis can be induced via MSC treatments, clinical benefit remains uncertain. The IA administration of MSC in animal models has led to non-integrated fibrous covering of osteochondral defects (OCD), but when administered directly to OCDs, it demonstrated well-integrated hyaline cartilage (Koga, 2008). Surgical management remains the gold standard of definitive treatment, which is imperfect. Limited hardware lifespan aside, joint incongruities following surgery can lead to "contact stresses up to 300% that of anatomic controls" (Phen & Shenker, 2019).

Independence and activities of daily living (ADL) require painless, mobile joints, with stiffness and pain reducing patient quality of life. Phen & Shenker (2019) attribute arthroplasty outcomes not only to complications and/or inevitable hardware failure, but also to the intrinsic alignment, stability, and congruity of the joint following intervention, features unique to each joint in question. Given that surgical intervention is often considered gold-standard care following acute intra-articular fracture, examples of surgical failure or revision exist, such as with the elbow (Jung, 2019) or hip (Verbeek, 2018).

If necessary, a "salvage procedure" of joint replacement is sometimes used, with expected limitations in joint function and subsequent ADL impairment following intervention. The ultimate goal of interventions rests in restoring anatomic alignment, stability, and congruence, and while surgical technique continues to improve, outcomes remain varied (Phen & Shenker, 2019).

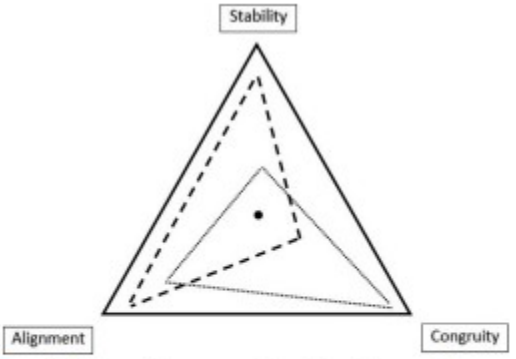

Fig. A Schematic representing the balance between congruity, stability, and alignment within articular joints. *Dotted line* represents an injured acetabulum. *Dashed line* represents an injured tibial plateau. Chronic cartilage injury affects the balance of joint congruity, stability, and alignment; however, this balance is *unique* to the joint in question.(Phen & Shenker, 2019)

Echoing the mantra of physical therapy and exercise

Repeated studies demonstrate improvement in joint pain, strength, and range of motion through these modalities. The following four prospective studies and one meta-analysis showed clear, universal, and significant improvements in pain, function, and quality of life. One randomized control trial of 40 patients, with a mean age of 78 (± 6 years), tested mobilization with movement (MWM) against sham therapy, measuring numeric pain rating scale (NPRS), hip flexion, internal rotation, and the three physical performance tests of timed up and go, sit to stand, and 40-meter self-paced walk test. MWM group pain rating decreased by 2 points with

improvements to hip flexion of 12.2 degrees, internal rotation of 4.4 degrees, and clinically significant improvements across all physical performance domains (Beselga, 2016). Another three-arm parallel group randomized trial of 188 patients with unilateral osteoarthritis (OA) of the hip were enrolled into patient education (PE), PE with manual therapy (MT), and MT alone groups to compare to a minimal control intervention group (MCI) to evaluate changes in NPRS following 12 sessions over six weeks. A clinically significant reduction in NPRS of 1.90 (95% CI 0.9-2.9) occurred in the PE with MT group over MCI group; this significant difference was maintained over 12 months of follow-up. There was no significant difference between PE and MCI groups, suggesting that patient education alone is insufficient for reductions in pain perception (Poulson, 2013). In comparing variance in force applied during MT, one randomized controlled trial of 60 patients with unilateral hip OA found significant ($p < 0.05$) increases in hip range of motion (ROM) (flexion: 10.6°, extension: 8.0°, abduction:6.4°, adduction: 3.3°, external rotation: 5.6°, internal rotation: 7.6°) in with high force mobilization relative to low-force mobilization and no significant difference between low-force and medium-force mobilization, suggesting utility in more aggressive manual therapy. Treatments consisted of three sessions of long-axis distraction mobilization in an open packed position with measurements of distraction force categorized as above (Estébanez-de-Miguel, 2018). In a study measuring short- and long-term clinical outcomes of MT for 15 unilateral hip OA patients, 8-week follow-up results showed universal and statistically significant improvements across several domains ($p < 0.5$) as follows: Harris Hip Scale (HHS), a 13-item patient/clinical report of pain, function, deformity, and ROM, scores improved from 60.3(±10.4) to 80.7(±10.5), Numerical Pain Rating Scale (NPRS) scores improved from 4.3(±1.9) to 2.0(±1.9), hip flexion range of motion (ROM) improved from 99 degrees (±10.6) to 127 degrees (±6.3) and hip internal rotation ROM

improved from 19 degrees (±9.1) to 31 degrees (±11.5) with improvements remaining significant ($p < 0.05$) at 29 week follow-up (Hando, 2012). One meta-analytic study concludes that physical therapy (PT) and/or exercise therapy (ET) significantly improve Western Ontario and McMaster Universities Arthritis Index (WOMAC) scores (a measure of function, stiffness, and pain) (Abbott, 2013). In effect, conservative physical therapies reduce pain, increase range of motion, and increase physical function.

Persistent joint dysfunction

Joint dysfunction is generally persistent with interventions in the conservative spectrum, such as pharmacolocial medications including oral nonsteroidal anti-inflammatory drugs (NSAIDs) and and other analgesics such as acetaminophen. When the combined therapies of PT, NSAIDs, and analgesics fail, intra-articular (IA) injections are often considered. Recent pathophysiological evidence suggests a blunted remodeling response may be responsible for the related chronic inflammation and resultant structural alterations of diseased joints. Matthiessen and Conaghan (2017) describe a positive feedback loop in synovial cell phagocytosis of IA cartilaginous debris, increased proteolytic enzyme release, and worsened inflammation. In this context, and within the bounds of this review, minimally invasive treatments include IA injections of corticosteroids, hyaluronic acid, and platelet-rich plasma.

Corticosteroid injections

Commonly used corticosteroids used in corticosteroid intraarticular injections (CSI), like triamcinolone or dexamethasone, are typically mixed with local anesthetics such as lidocaine or bupivacaine to help provide some immediate relief. These treatments are effective tools for damping IA inflammation in most cases, with arthralgia and articular dysfunction improvements varying in both degree and duration across patient populations (McCabe, 2016). In a study

evaluating the efficacy of IA hip CSI, 78 patients underwent fluoroscopic guided injection and were divided into response categories of no relief, immediate relief (<2 weeks), and continued relief (>2 weeks). Seventy-eight patients, a total of 82 injections, were assessed with 16 (19.5%) showing no response, 39 (47.6%) showing immediate response, and 27 (32.9%) showing continued response. The patient sample was then evaluated for demographic correlations across age, BMI, Tönnis grade (degree of OA severity assessed by imaging), or prior symptom duration. Advanced Tönnis grading was strongly associated ($p = 0.002$) with subsequent surgical intervention with 38 (48.7%) patients having done so within two years of CSI (Lai, 2018). Another retrospective study evaluated CSI benefit over time, including 113 patients of mean age 59 (±13.7 years) with Tönnis grading ≥ 1 undergoing image-guided hip CSI with evaluations of EuroQol-5 domain (EQ5D - constituting mobility, self-care, return to activities, pain/discomfort, and anxiety/depression). This was further examined with the EQ5D-visual analog scale (VAS) which is grading pain on a linear spectrum. Other measures included hip disability and osteoarthritis outcome score (HOOS), a 40-item extension of WOMAC as above) obtained before CSI, less than eight weeks from CSI, and 8-24 weeks from CSI. There was no significant change for any patient at any interval in EQ5D ($p = 0.450$, 0.770, 0.493), EQ5D-VAS ($p = 0.581$, 0.915, 0.455), or average-HOOS ($p = 0.478$, 0.696, 0.443) scores. Forty-nine of 113 patients received surgical intervention within one year, with positive correlation in days from injection to surgery and degree of change in EQ5D ($r = 0.29$, $p = 0.025$), average-HOOS ($r = 0.33$, $p = 0.019$), and total-HOOS ($r = 0.37$, $p = 0.008$) (Walter, 2019).

CSI injections are not without serious risk. One retrospective study of 70 patients, with an average age of 67 (±17 years), undergoing CSI of a hip mean were followed for 3-12 months. The study revealed dramatically higher rates of femoral head collapse (p=0.002) with

corticosteroid injection (17%) versus no-injection (1%) groups (Simeone, 2019). Another retrospective study examined rapid destructive osteoarthritis (RDOA) and total hip arthroplasty progression, noting 1-in-5 CSI patients acquiring RDOA with a mean time to total hip arthroplasty of 10.2 months relative to 24.9 months without (Hess, 2018). Infection rates may also increase, as another retrospective study of 456 patients demonstrated, with significantly increased risk for patients receiving more than one injection (2% of single-injection patients and 6.6% of multi-injection patients; $p = 0.04$; odds ratio 3.30) following THA (Chambers, 2017).

Hyaluronic acid

Naturally found within joint space, hyaluronic acid (HA) serves as lubrication for joints and contributes to cellular regulation (Ayhan, 2014). In the degenerative progression of joint disease, concentrations of HA decrease. It is important to note that HA products vary in their specifications, augmented by mannitol, consisting of low or high molecular weight, and there is a postulation that low molecular weights are associated with later stages of degenerative joint disease (Band, 2015). One prospective study of 226 patients greater than 40 years of age with uni- or bilateral hip arthralgia and partially preserved joint space were treated with ultrasound-guided IA and were evaluated via WOMAC and HHS at three month intervals for three years. No patients received subsequent HA injections or surgical interventions. There were no adverse effects registered across the entire study during this time, and significant (*p*

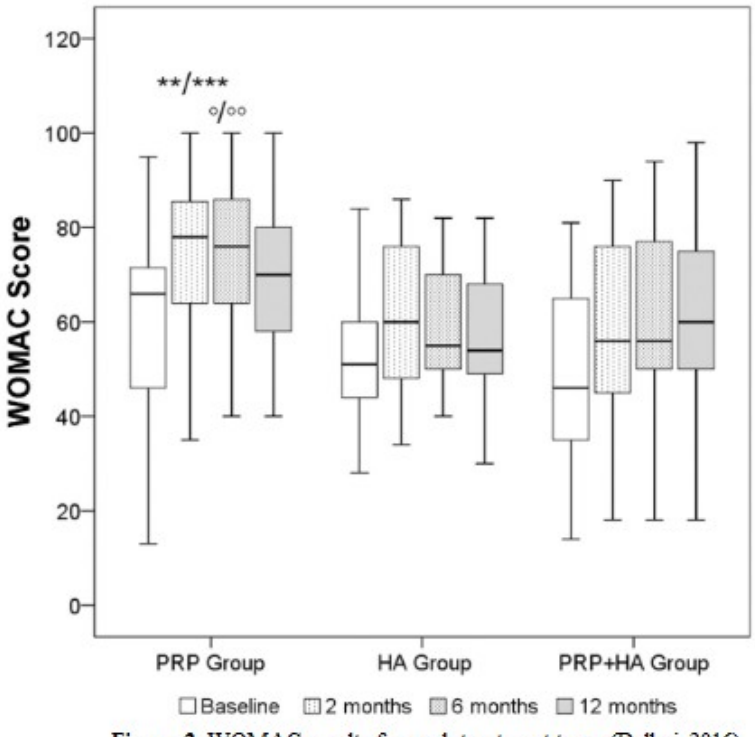

Figure 3. WOMAC results for each treatment type. (Dallari, 2016)

< 0.001) improvements from baseline WOMAC (WOMAC_T0 mean 62.20±1.973; WOMAC_T3 52.86±1.782; WOMAC_T6 48.05±1.780; WOMAC_T12 50.34±2.017) and HHS (HSS_T0 57.36±1.716; HSS_T3 70.16±1.646; HSS_T6 75.13±1.515; HSS_T12 72.50±1.710) were observed in all patients at all intervals following treatment. The maximal benefit was demonstrated in participants beginning with Stage 2 degenerative OA per Kellgren-Lawrence staging (Pogliacomi, 2018).

Examining HA injection in concert with PT, one prospective study by Mauro, Sanfilippo, & Scaturro (2017) found significant benefits in pain score, hip disability, daily function. This combination lowered NSAID intake by administering three ultrasound image-guided injections of HA 45 days apart to 40 subjects (65 hip CSI's) of mean age 61 (±11 years) who then participated in three weekly sessions of physical therapy to a limit of ten weeks. VAS with an activity baseline of mean 6.94 (±2.053) improved to 1.46 (±1.3973) over the duration of the study. Hip ROM improvements by the end of the study ($p < 0.001$): flexion improved 16.23°±8.884; extension improved 8.00°±7.385; abduction improved 11.15±6.298; improved 11.77°±8.359; improved 8.69°±6.267. Mean Lequesne index value (a measure of daily function) of 12.9±4.2164 improved progressively to 5.5±2.5731 by the study end ($p < 0.001$). NSAID consumption was measured as a percentage of participants taking it to manage pain from the start to end of the study, which improved from 60% to 55%, respectively. Treatment was well-tolerated, with three documented mild and transient adverse events (Mauro, 2017).

When compared to glucocorticoid injection, one double-blind, randomized trial by Tammachote et al. (2016) found the two similarly effective, though HA benefit came with significant temporal delay. This prospective, randomized, double-blind clinical trial selected 99 participants with symptomatic knee OA who were then randomized to receive IA HA or CSI,

measuring knee pain severity, function, and ROM at six months. Treatment groups ultimately had similar improvements in knee pain, knee function, and range of motion ($p < 0.0001$). End-study mean differences: VAS 3 (95% CI; -6 to 11), WOMAC 0 (95% CI; -8 to 6), flexion -1° (95% CI, -5° to 2°), and extension 0° (95% CI, -0.5° to 0.5°). Significantly, score improvements in CSI group occurred sooner, with mean outcome at 24 hours of VAS 12 (95% CI; 5 to 20; $p = 0.002$) and at 1 week of VAS 9 (95% CI; 1 to 15; $p = 0.018$). Mean outcome differences continue to shrink at two weeks with no significant terminal differences between groups (Tammachote, 2016). HA efficacy relative to controls is further confounded, as one large randomized/double-blinded trial of 357 participants (Brander, 2019) in agreement with a 6-study meta-analysis (Wu, 2017) demonstrated no significant improvements in walking pain, hip pain, or overall patient function when comparing HA injections against controls. Patient sampling may explain these results, as one systematic review of 25 randomized double-blinded studies (Piccarilli, 2016) suggested the most significant benefit of HA injections occurred in those with mild to moderate OA severity.

Platelet Rich Plasma

In the realm of regenerative medicine, platelet-rich plasma (PRP) therapies have gained ground, consisting of any autologous blood that contains a higher concentration of platelets from baseline (Urits, 2020), with harvested concentrations varying from patient to patient or centrifuge to centrifuge. Physiologically, these platelet concentrations are thought to secrete growth factors, enhance chondrocyte proliferation, and improve collagen deposition (Visser, 2009). Similar to HA, these treatments appear to be maximally beneficial in early degenerative stages (Kraeutler, 2016). In one randomized, blinded clinical trial involving three parallel groups, IA HA and PRP were compared together and apart with synergistic outcomes, though when isolated, PRP

produced more durable results than HA or in combination with HA. A total of 111 adult participants not more than 65 years of age with hip OA and VAS pain intensity of 2-10 were recruited. Exclusion criteria included extensive deformity, surgical history, or the presence of infectious, rheumatic, cardiovascular, or autoimmune disorders. Outcomes were measured at two, six, and 12 months across WOMAC, VAS, and HHS. Participants were randomly assigned to one of three groups to receive three weekly injections of either HA, PRP, or PRP+HA, with some significant initial difference in VAS scores between groups, with PRP group scoring lowest. Subsequent PRP VAS scores remained lowest throughout follow-up, and there were no complications related to treatment apart from transient pain from administration in 13 individuals. Within this study, baseline WOMAC, VAS, and HHS scores were provided graphically (figures 1-3), but two-month to six-

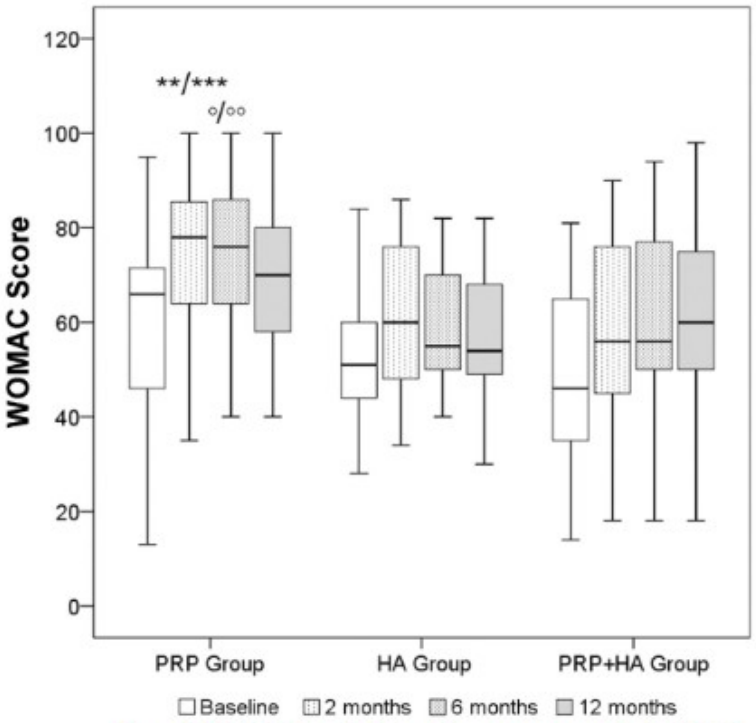

Figure 3. WOMAC results for each treatment type. (Dallari, 2016)

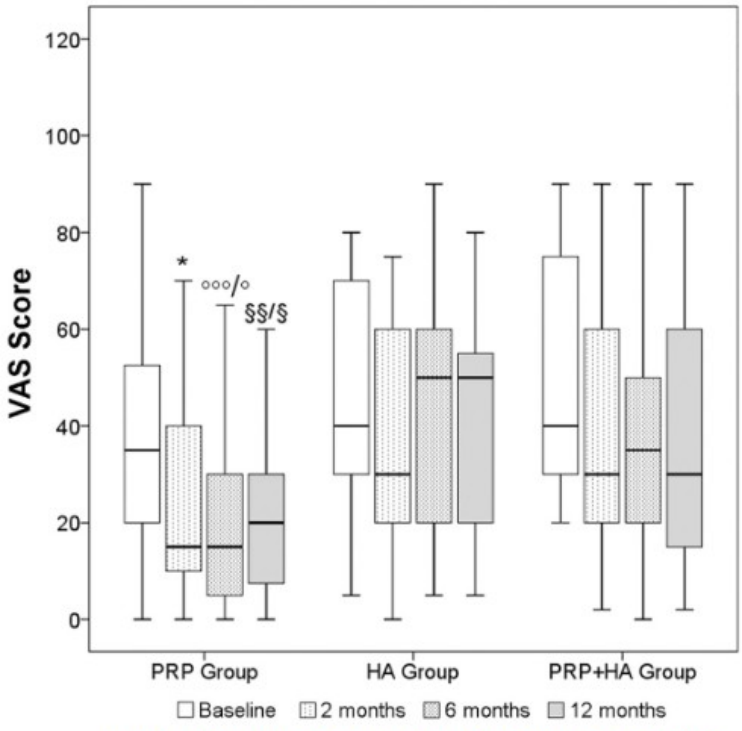

Figure 1. Visual analog scale scores for each treatment type. (Dallari, 2016)

month follow-up results are as follows: HA two-month to six-month WOMAC 59 to 59; HA two-month to six-month VAS 38 to 44; PRP two-month to six-month WOMAC 73 to 72; PRP two-month to six-month VAS 23 to 21; PRP+HA two-month to six-month WOMAC 59 to 59; PRP+HA two-month to six-month VAS 35 to 35. Twelve-month follow-ups lost statistical significance among WOMAC scores in this study, leaving VAS results as the only meaningful trend as follows: PRP 24, HA 42, and PRP+HA 38. The authors conclude that improvements were achieved in reducing pain, ameliorating quality of life, and facilitating functional recovery (Dallari, 2016).

Modeled on Dallari et al.'s work from 2016, a more recent randomized clinical trial consisting of three parallel groups, IA, HA, and PRP, were compared together and apart. Ninety-two patients of 60.93±4.54 years of age with grade 2-3 hip OA were randomly divided into HA, PRP, and HA + PRP treatment groups with no significant differences in group demographics or pre-treatment score results. In each group, two ultrasound-guided IA injections two weeks apart were administered to the affected hip with measurements at two and six months post-procedure. Treatment complications in 17 patients across the study consisted of warmness, stiffness, and heaviness, with no significant difference in incidence across groups ($p = 0.838$). Results ($p < 0.001$) as follows: HA baseline-to-terminal WOMAC 41.41±11.52 to 27.21±9.25; HA baseline-to-terminal VAS 8.10±1.18 to 3.90±1.4; HA baseline-to-terminal Lequesne 12.52±2.18 to

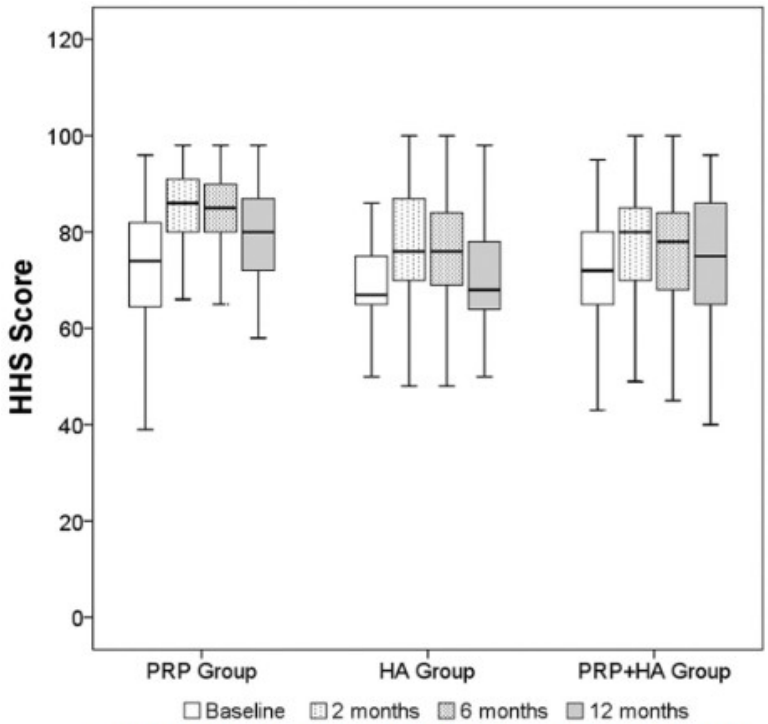

Figure 2. Harris Hip Score results for each treatment type. (Dallari, 2016)

10.29±2.82; PRP baseline-to-terminal WOMAC 41.39±9.36 to 21.53±10.40; PRP baseline-to-terminal VAS 7.63±1.31 to 3.13±1.29; PRP baseline-to-terminal Lequesne 12.20±2.18 to 8.59±2.99; PRP+HA baseline-to-terminal WOMAC 41.16±8.13 to 21.16±8.00; PRP+HA baseline-to-terminal VAS 8.00±1.18 to 3.13±1.18; PRP+HA baseline-to-terminal Lequesne 12.45±1.66 to 8.08±2.55. The authors conclude that PRP produced greater improvements than HA when isolated, but they were ultimately most efficacious when combined. (Nouri, 2022).

In a separate retrospective study by Koch et al. (2018), intraligamentous PRP injections via knee arthroscopy were evaluated with efficacy measured by clinical, objective, and functional performance assessments. Selected intraoperatively, participants met inclusion criteria of partial rupture of the anteromedial, posterolateral, or both ACL bundles, while exclusion was based on criteria such as a complete tear of at least one bundle, previous or concurrent major cartilaginous or ligamentous reconstruction/repair, autoimmune/inflammatory disease, or follow-up reconstruction. Of the 42 patients selected, 38 remained after exclusion criteria were applied. Participants had a mean age of 42.8 (±13.5 years), with a total of 25 right knees, 13 left knees, and 30 dominant side knees that were included. All patients received intraligamentous PRP injection without comparison or control group; the study was not blinded. Extensive measurements were taken through patient satisfaction, return to sport (RTS) time, post-operative complications, clinical scores of Lysholm, Tenger, Cincinnati, and Marx Activity Scales, clinical examination by rolimeter assessment and clinical stability testing (Lachman, pivot shift test). Functional performance was tested by drop-jump, side-hop, one- and two-leg stability, and quick-feet tests were performed, with failure defined as persisting knee instability indicating ACL reconstruction, a side-to-side difference greater than 4mm in rolimeter analysis of knee joint, and/or persisting positive pivot shift test/no firm endpoint in lachman-testing in follow-up

evaluation. Four participants were ultimately excluded from the results as above, with one additional participant excluded due to Achilles tendon rupture during the follow-up period. Two additional participants were excluded due to a complete rupture in the index knee after ACP treatment, requiring premature ACL reconstruction. The mean RTS was 5.8 months (SD 3.6), and full sportive activity was regained by 71.1% of patients with a subjective report of mean RTS at 85.8%±19% of preinjury level. Rolimeter testing improved from preoperative 1.9mm ±1.4 to 0.6mm ±1.8 and activity scoring revealed near complete recovery of functional activity levels through Lysholm, Tenger, Cincinnati, Marx Activity Scale assessments. There was no significant difference between index and healthy knee post-operatively to drop-jump, side-hop, one- and two-leg stability, or quick-feet testing throughout the study population. Outcomes were considered satisfactory following intraligamentous PRP application with a low failure rate and a high percentage of return to sportive activity. However, these results have potential for bias as materials were provided by commercial PRP manufacturer, "Arthrex" (Koch, 2018).

A Step Forward: Mesenchymal Stem Cells

Beyond the utilization of PRP stands a cellular therapy of growing repute: Mesenchymal Stem Cell (MSC) therapies. The specific constitution and site of intervention in these treatments vary, making comparison across this treatment class difficult at best. MSC therapies may be autologous or allogeneic, expanded or non-expanded, mixed with other tissue types such as bone marrow aspirates, or administered intra-articularly or within subchondral bone. Commonly harvested from either bone marrow or adipose tissue, MSCs are thought to differentiate and mature into numerous cell lines, contribute to the coordination of tissue remodeling, modulate inflammation, and stimulate angiogenesis (Pak, 2018).

In one study of outcomes using expanded *ex vivo* samples taken to undergo rapid cellular division to increase MSC quantity and concentration before administration and autologous bone marrow-derived MSC (BM-MSC) treatments in patients with hip OA, participants demonstrated significant reductions in pain, stiffness, function, and ROM. In this small prospective study, ten patients with a mean of 60 years of age, Tönnis-graded uni- or bilateral hip OA refractory to analgesics, HA, or CSI, were evaluated before and after treatment IA three treatments one week apart of 20 x 10^6 BM-MSC cells per dose, assessing VAS, HHS, and WOMAC before and after. Pre-treatment VAS of 4.2+0.5 improved to 1.1 ±0.3 ($p < 0.0001$). Pre-treatment WOMAC of 34.5 ±8.2 improved to 19.2 ±6.1 ($p < 0.15$). Pre-treatment HHS of 61.9±3.9 improved to 85.7 ±3.9 ($p < 0.003$). WOMAC scores

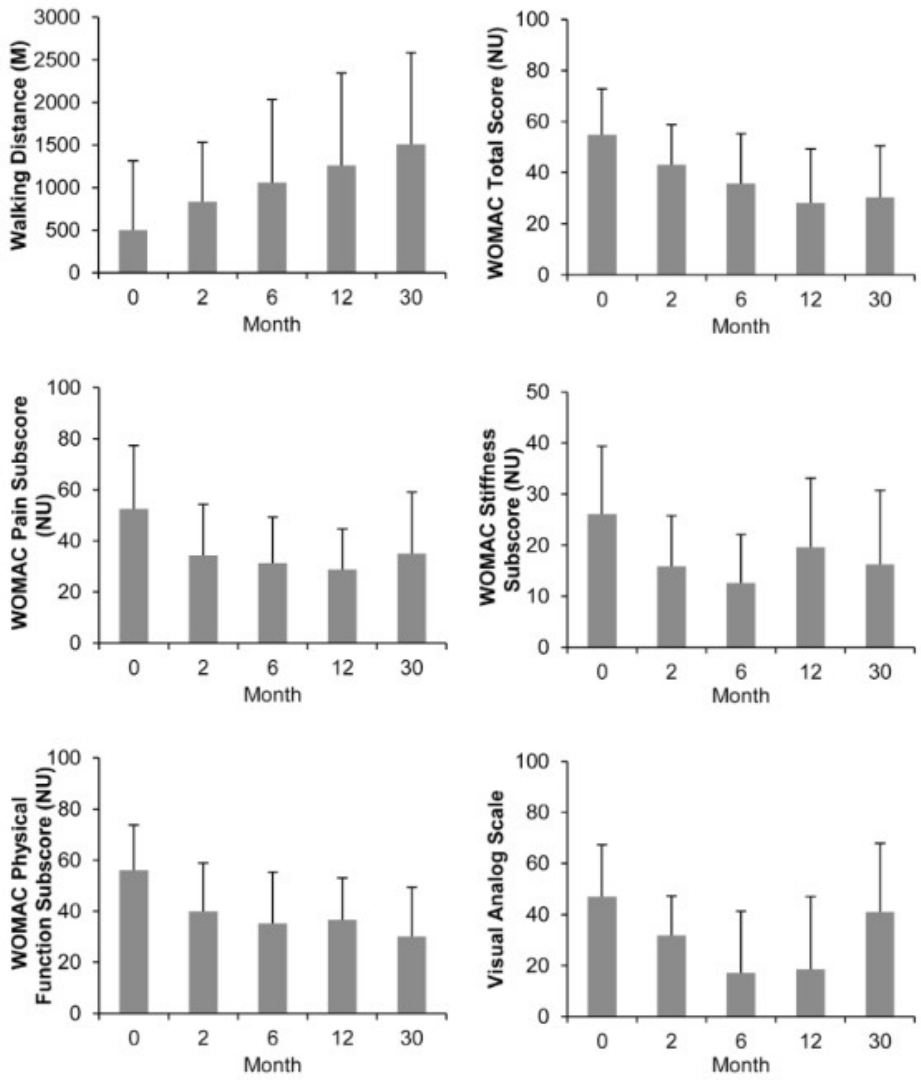

Figure 4. Change from baseline in clinical parameters in all osteoarthritis patients. (Emadedin, 2015)

improved, but not significantly. VAS and HHS scores both showed significant improvement. Tönnis grading pre- and post-treatment suggested slowing OA progression (Mardones, 2017).

A combined report of 3 independent studies (knee, ankle, and hip OA, respectively) evaluated the benefit of single-dose expanded autologous BM-MSC and found similar results. In this small prospective study series of expanded BM-MSC IA treatments, 18 combined patients with aforementioned joint OA were evaluated by self-report (VAS), clinical evaluation (WOMAC, HHS, Foot and Ankle Outcome Score (FAOS), MRI, and laboratory testing following treatment at two, six, 12, and 30-month intervals. Of the six hip patients, one was lost to follow-up secondary to traumatic injury. All joint groups significantly improved walking distance ($p < 0.008$). WOMAC sub-scores improved throughout. Mean VAS scores improved at six (47.0 vs. 17.0; $p < 0.001$) and twelve (47.1 vs. 17.1, $p < 0.002$) months, rebounding at 30 months in all joint groups (Figure 4). Imaging outcomes observe reduced subchondral edema in three of six knee OA and four of six ankle OA patients. Three of five hip OA patients demonstrated articular cartilage repair (Figure 5). No changes in laboratory markers were found

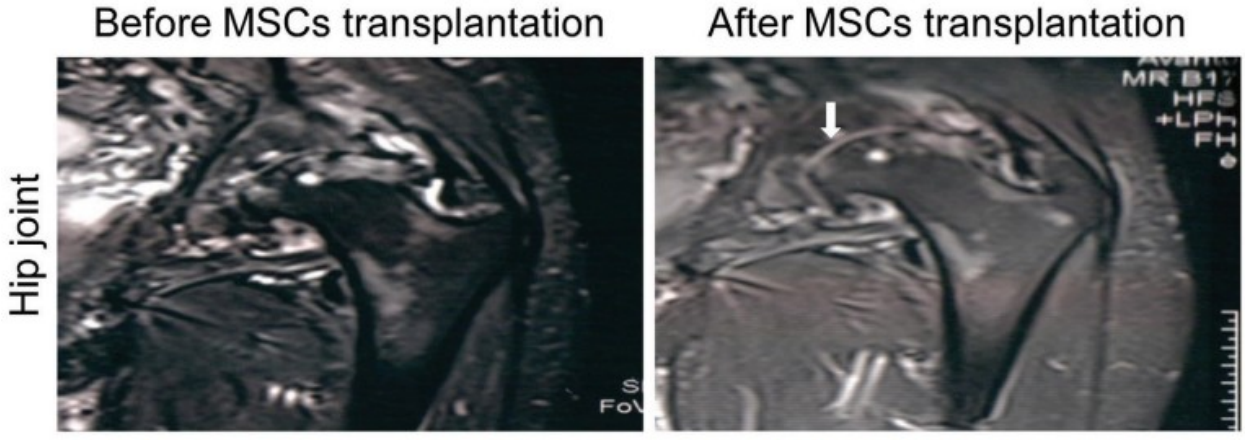

Figure 5. MRI analysis. (A) Sagittal T2 weighted MR image of patient with hip OA shows cartilage surface before MSC transplantation (arrow). (B) Note the predominant increase in cartilage thickness after MSC transplantation (arrow). (Emadedin, 2015)

at any interval. There were no serious adverse events, with few minor localized reactions such as rash or erythema (Emadedin, 2015).

Hernigou et al. produced an evaluation of Mesenchymal Stem Cell Therapy (MSCT) in the treatment of bilateral knee osteoarthritis in 2021. They focused on comparing MSCT of the subchondral bone and the intra-articular space and the site selection's relative effect in delaying or avoiding Total Knee Arthroplasty (TKA). This prospective study included the inclusion criteria of bilateral knee pain due to medial knee osteoarthritis graded 1-4 on the Kellgren-Lawrence scale, which did not respond to conservative therapies or injection therapy for at least six months. Participants were excluded if they had any prior history of knee surgery or any evidence of rheumatological or systemic disease, diabetes, malignancy, or infection (Hernigou et al., 2021). All participants were at least three months out from any IA injections. There were a total of 60 participants with 120 knees compared. Demographics included patients between 48 and 72 years of age, with a mean of 61, and follow-up was conducted on patients aged 62-87, with a mean of 76 years of age. No restrictions on gender or ethnicity were placed, and the study concluded with 23 male participants and 35 female participants. The BMI of the study group was monitored, and participants fell between 20.4 and 32.5, with a mean of 28.1. Participants were divided into intra-articular (IA) groups and subchondral (SC) groups by blind selection of envelopes, which dictated group assignment. Demographics between groups were not evaluated, but were instead compared by symptom quantification. The study was blinded and there was no control group. Study endpoints were evaluated by measuring Pain Score (a visual analog scale or VAS) and Knee Society Score (a standardized form for subjective reporting). Clinical outcomes were measured/taken by orthopedic research fellows at intervals: three months out, six months out, then annually over 13-18 years using MRI and augmented by software assessment of cartilage volume and synovitis. Results at 15 years indicated a yearly arthroplasty incidence of 1.3% per knee year for the SC group and 4.6% per knee year for the IA group ($p = 0.01$). Twenty

percent of SC knees and 70% of IA knees underwent TKA. Among the 18 patients who had no subsequent TKA on either knee, all preferred the knee that underwent SC. The authors concluded that implantation of MSCs in the subchondral bone of an osteoarthritic knee is more effective in postponing TKA than [IA] injection of the same intra-articular dose (Hernigou et al., 2021). The study's strengths include a double-blind design with independent review and augmentation by an impartial software analysis of benefits. Strengths further include a sufficiently large sample size, inclusion criteria based on standardized measures of dysfunction, and its span over 12-18 years. Study weaknesses include a potential for bias when utilizing an orthopedic fellow for the evaluation of treatment effects or may be found in the study's demographics which were not evaluated. No conflicts of interest are declared.

Bąkowski et al. (2021) demonstrated a differential benefit of mesenchymal stem cell therapy (MSCT) via autologous adipose tissue (AAT) treatment in the knees of osteoarthritis (OA) patients. Adipose tissue serves as a large reservoir of mesenchymal stem cells (MSCs) and was used as the source for MSCT in this experiment. This prospective study evaluated 37 patients with uni- or bilateral knee OA as measured by clinical history, physical exam, and X-ray imaging. Each had received a single intra-articular (IA) injection of AAT to one or both knees and were followed over a period of 27 $\pm$ 6.5 months. Patients were 57.78 $\pm$ 7.39 years old and consisted of 16 males and 21 females with a BMI of 21.30 $\pm$ 7.51. Ethnicity was not considered. Intervention was comprised of lipoaspiration of subcutaneous adipose tissue yielding ~10mL AAT per treatment. Participants were grouped by Kellgren-Lawrence (K-L) OA classification and further divided by later treatments of IA hyaluronic acid (HA), platelet-rich plasma (PRP), knee arthroscopy, or partial/total knee arthroplasty (TKA) at follow-up. This study was not blinded and there was no control group. Endpoints measured Pre/Post Knee Injury and

Osteoarthritis Outcome Score (KOOS), Pre/Post International Knee Documentation Committee 2000 (IKDC 2000), Pre/Post Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Pre/Post Health Questionnaire EQ-5D-5L, Pre/Post Numeric Rating Scale (NRS) of Joint Pain, and Subjective Satisfaction Scale (SSS): 0 (unsatisfied) to 10 (very satisfied). Results demonstrated significant differences in pre- and post-treatment scores for NRS, WOMAC, KOOS index, and EQ-5D-5L index. SSS was 6.16 +- 3.07. There was no significant difference between satisfied and unsatisfied patients with respect to BMI and NRS scoring. 6 of 7 patients with K-L stage IV OA were unsatisfied with AAT treatment. The authors concluded that of all groups, K-L stage II OA patients with normal BMI were most likely to report benefit from AAT and that KL stage IV OA patients would report no benefit. No adverse events were reported at the donor or treatment sites. Strengths of the study include follow-up interval, controls for subsequent treatments preceding follow-up, a sufficiently large N value, group categorization by standardized measures of dysfunction, and generalizability to the broader public. The weaknesses of the study include absent placebo comparison, lack of evaluation of the effect of intergroup BMI, and subjectivity in satisfaction scoring. No conflicts of interest are declared.

Freitag et al. (2020) demonstrate hyaline cartilage repair in the knee joints of 18 males and nine females with Grade IV (Kellgren and Lawrence grading system) between the ages of 32-63 (mean 53.6 +- 6.7) with a BMI mean of 27.7 (+- 5.3). Their prospective research answered the question of the safety and efficacy of adipose-derived mesenchymal stem cell (ADMSC) therapy in combination with arthroscopic abrasion arthroplasty (AAA) in advanced knee osteoarthritis (OA). All participants had attempted conservative treatment, including analgesia/anti-inflammatory medication, physical therapy/weight management, and bracing. Surveys were conducted in English for which all participants were proficient. Candidates were

excluded if pregnant, breastfeeding, currently had cancer or other serious underlying pathology, had a history of significant organ impairment or failure, a history of inflammatory arthropathy, or allergic history to treatment agents. Ethnicity was not considered.

Intervention is described as the application of 50 million ADMSCs injected within one week of AAA with repeat injection at six months. This case series had no control group and was not blinded. Study endpoints evaluated safety and tolerability, pain and functional measures (Numeric Pain Rating Scale (NPRS), Knee Injury and Osteoarthritis Outcome Score (KOOS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and the Patient Global Impression of Change (PGIC)), and MRI analysis including MRI Observation of Cartilage Repair Tissue (MOCART) score and T2 relaxation time mapping for the typing of cartilage regenerated.

Results for 26 of 27 patients (one failing treatment at 12 months with Total Knee Replacement (TKR) at that time) were evaluated through One-Way Repeated Measures ANOVA over six, 12, 24, and 36-month data points. NPRS improved from a mean of 5.6 ($\pm$ 2.7) at baseline to a mean of 1.5 ($\pm$ 1.4) at 36 months - a 73.2% improvement in NPRS against baseline | ($r = 0.082$; $p < 0.001$). KOOS Quality of Life subscale improved by an average of 119.1%. KOOS sport and recreation subscale improved by 161%. Global WOMAC score correlates with an improvement of 55.2%. 92.5% of patients reported satisfaction greater or equal to "much improved." 89.5% of participants achieved a minimally clinically important difference (MCID) at 36 months.

Structural outcomes (MR) were assessed at 12 and 36-month follow-ups. One participant was excluded at 12 months due to a spinal implant. Of the 26 patients imaged at 12 months, 21 had further MRIs at 36 months. MOCART (out of 100) mean score of 73.7 and 75.5 at 12 and 36 months, respectively. Of 26 participants, 18 had MRI T2-weighted imaging performed at 12 months and 14 at 36 months. The overall average indicated progressive maturation of regenerative cartilage (41.7ms and 40.0ms, respectively). Significantly, of two individuals with initial varus angulation, radiological assessment confirmed a correction of 3 and 3.1 degrees after 12 months. There were no complications or adverse events; expected symptoms resolved well through ice and oral analgesics/nonsteroidal anti-inflammatories over course of treatment.

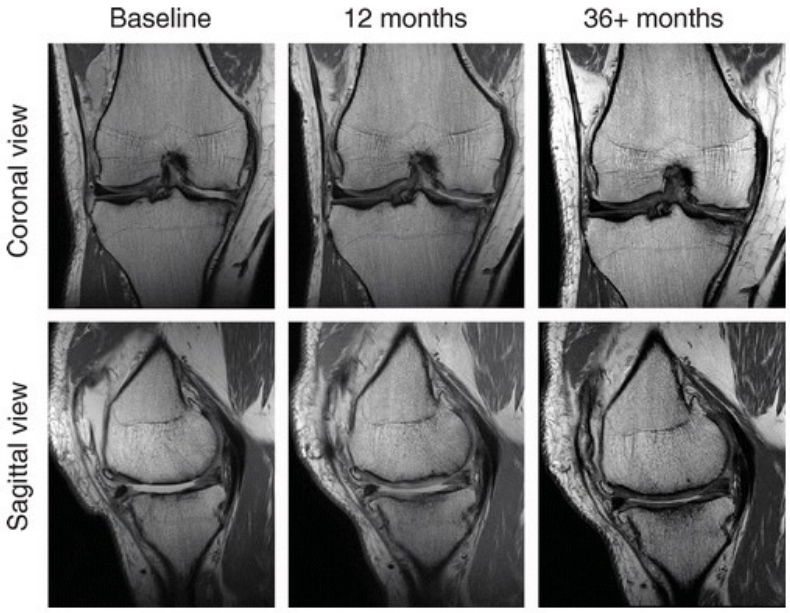

Figure 6. Sequential coronal and sagittal MRI proton density images of participants knee at baseline, 12 and 36+ months. (Freiteg, 2020)

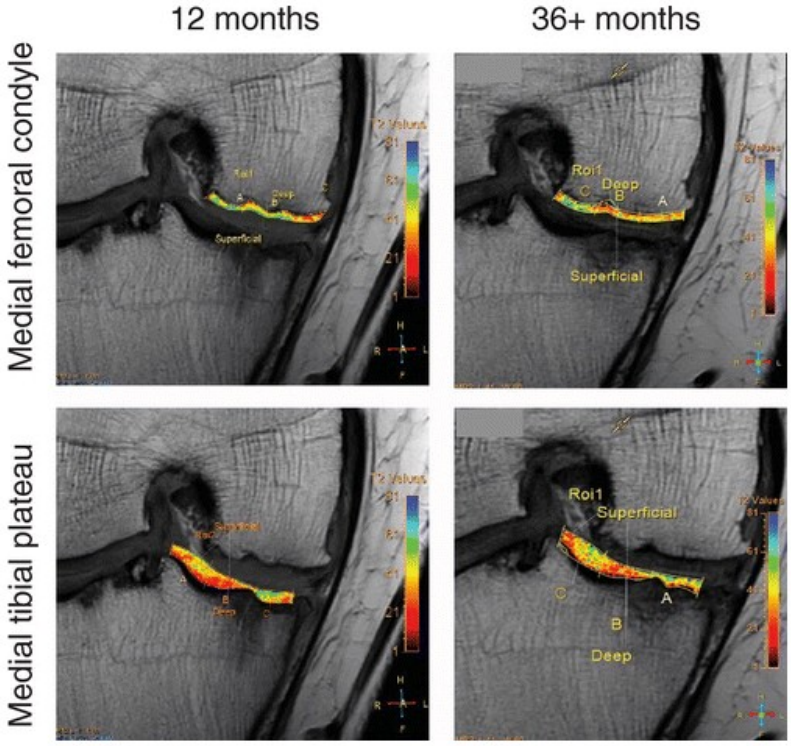

Figure 7. Example of sequential MRI T2 mapping of the area of cartilage regeneration at 12 and 36+ months. (Freiteg, 2020)

Freitag et al. conclude that combined stem cell therapy and keyhole knee AAA in advanced OA reliably produces reduced pain, increased function, and regrowth of cartilage in the knee. T2-weighted imaging indicates regeneration of hyaline-like cartilage, and that treatment was well tolerated with no related serious events. MRI analysis demonstrated failed chondral regeneration in areas that were not abraded, suggesting necessary disruption of arthritic sclerotic subchondral bone to the point of capillary bleeding as necessary for resultant migration and proliferation of bone marrow-derived MSCs.

The study's strengths include exclusion criteria for smokers and diabetics, a sufficiently large sample size, multiple instruments for outcome evaluation, objective evaluation through MRI techniques, and length of follow-up. The weaknesses of the study include the case series nature and lack of a control group, though the authors observe past research assessing AAA in isolation, which leads to early conversion of total knee replacement within 2-5 years. This single-group study does include some subjective measures, but the breadth of instruments ameliorates some of these concerns. The authors note that the histopathological assessment of regenerative cartilage would be definitive, but they cite T2-weighted imaging as validated and non-invasive. There are no conflicts of interest declared.

Discussion

Independence and activities of daily living (ADL) require painless and mobile joints. Conversely, stiffness and pain reduce the patient's quality of life, worsen the progression of diseases such as diabetes, cardiovascular disease, obesity, and impaired sleep (Phen & Shenker, 2019). Treatment of arthropathies relies on a spectrum of treatments with increasingly risky and consequential outcomes.

Physical therapy repeatedly demonstrates benefit (Beselga, 2016; Poulson, 2013; Estébanez-de-Miguel, 2018; Hando, 2012; Abbott, 2013), but must be administered at intervals and while supervised for the sake of compliance and outcome (Poulson, 2013). Persistent arthralgias not responding to conservative measures often come with degenerative progression (Matthiessen & Conaghan, 2017), with later interventional escalations as with intra-articular injection.

In the minimally invasive realm, corticosteroids are often considered first line and patient response is highly variable (McCabe, 2016). Substantial percentages of patients receive limited or no benefit from corticosteroid injection (Lai, 2018; Walter, 2019), and substantial numbers advance to surgical intervention within one year (Walter, 2019). These uncertain benefits come with an increased risk of infection (Chambers, 2017), chondrotoxicity, accelerated degeneration, and rapid destructive osteoarthritis (Hess, 2018).

Considering these risks, alternatives such as hyaluronic acid and platelet-rich plasma may be appropriate. In the case of hyaluronic acid, multiple studies showed benefit (Pagliocomi, 2018; Mauro, 2017; Tammachote, 2016), with others casting doubt (Brander, 2019; Wu, 2017). The degree of benefit appears comparable with corticosteroids (Tammachote, 2016) but with fewer adverse effects (Pagliocomi, 2018; Mauro, 2017; Tammachote, 2016). Perhaps a step more reliable and efficacious, platelet-rich plasma therapies are reasonably common (Urits, 2020) and very well tolerated (Dallari, 2016; Nouri, 2022). Thought to secrete growth factors, enhance chondrocyte proliferation, and improve collagen deposition (Visser, 2009), these autologous treatments have repeatedly demonstrated improvements in pain and function (Dallari, 2016; Nouri, 2022; Koch, 2018).

Of question, then, is cell therapy. More invasive than drawing blood and requiring autologous sampling of marrow or adipose tissue, mesenchymal stem cells are thought to differentiate and mature into several different cell lines, modulate inflammation, contribute to the coordination of tissue remodeling, and stimulate angiogenesis (Pak, 2018). Though studies were small, Mardones (2017) and Emadedin (2015) demonstrated improvements in pain, function, and structural regeneration using autologous, bone marrow-derived mesenchymal stem cells. Expanded adipose-derived mesenchymal stem cells also appear effective, with improvements in pain, function (Bąkowski, 2021; Freiteg, 2020), and structural regeneration and angular defect correction (Freiteg, 2020) evident in other small studies. These treatments appear safe, without any serious adverse events (Mardones, 2017; Emadedin, 2015; Hernigou, 2021; Bąkowski, 2021; Freiteg, 2020). As with platelet-rich plasma injections, small numbers of patients experienced transient localized symptoms (Mardones, 2017; Emadedin, 2015). Finally, one study suggested that the target of administration may be significant, as subchondral injections in the knee demonstrated better postponement of total knee arthroplasty relative to intra-articular injection (Hernigou, 2021).

Conclusion

The management of joint dysfunction presents a complex challenge, as it directly impacts patients' independence and activities of daily living while also contributing to the progression of various comorbid diseases. This review underscores that importance while also highlighting the many risks and uncertain benefits of commonly used interventions in the realm of orthopedics.

Physical therapy remains the cornerstone of conservative orthopedic management, offering consistent benefits when supervised and administered at appropriate intervals. From there, the spectrum of treatment widens, as do the risks associated with each treatment modality.

After NSAIDs and analgesics fail, a common next step is intra-articular corticosteroid injection, despite their variable efficacy and chondrotoxicity. Alternative therapies such as hyaluronic acid and platelet-rich plasma demonstrate a lower risk profile, offering similar benefits with potentially fewer adverse effects. Unfortunately, like the steroid injection, evidence is mixed for a reliable response to treatment.

Representing a promising avenue for orthopedic management, mesenchymal stem cells show remarkable regenerative results. Their studies remain small and infrequent, with few controls or blind comparisons. Significant demand exists for further well-designed studies to establish long-term efficacy and safety in these emerging technologies.

As postulated by Phen and Shenker (2019), orthopedic practices require a tailored approach that considers the individual patient's anatomy, personal needs, and the availability of evidence-based interventions. Continued research is warranted in supporting and refining existing treatments and exploring novel therapeutic modalities to enhance the quality of life for the many patients suffering from joint dysfunction and disease.

Applicability to Clinical Practice

Corticosteroids, while a powerful and inexpensive tool in the treatment of arthralgia, come with consequences that patients pay in accelerated degeneration and symptom progression over the months and years that follow. Proving equally reliable and effective alternative therapies such as hyaluronic acid and platelet-rich plasma treatments should be considered. Contrasting platelet-rich plasma, hyaluronic acid injections are shelf-stable and involve no harvest requirements or lengthy centrifugation process. As such, providers in the clinical setting may consider hyaluronic acid a lower-risk alternative to corticosteroids for persistent joint pain and dysfunction refractory to conservative measures. The review of therapies above demonstrates a

needed shift from intra-articular injections for the treatment of arthropathy. While the above treatments help delay surgical intervention, definitive treatment is unlikely to be found using mesenchymal stem cells, given the equipment, laboratory, and imaging requirements.

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