Journal of Regenerative Biology and Medicine

ISSN: 2582-385X
Leung S, et al.,2023-J Regn Bio Med
Research Article

The Effects of Autologous Stem Cells from Bone Marrow and Adipose Tissue on Patients with Knee Osteoarthritis

Stephanie Leung[1], Afroze Khan[2] and Ana Arias[3], Paul Eliot Hughes[4*]

[1]BS, College of Osteopathic Medicine, California Health Sciences University, Clovis, California, United States

[2]BA, Hughes Orthopedics, San Mateo, California, United States

[3]LVN, Hughes Orthopedics, San Mateo, California, United States

[4]CEO, MD, Hughes Orthopedics, San Mateo, California, United States

[*]**Corresponding Author:** Paul Eliot Hughes, CEO, MD, Hughes Orthopedics, San Mateo, California, United States.

Received date: 05-07-2023

Accepted Date: 06-05-2023

Published Date: 08-09-2023

Abstract

Osteoarthritis (OA) of the knee joint, the most common form of knee arthritis, is the gradual degeneration of joint cartilage. A progression of OA is characterized by the degradation and degeneration of the articular cartilage with subchondral bone remodeling, osteophyte formation and inflammation leading to bone-on-bone contact causing pain, stiffness, and functional difficulties and disability. OA affects the patient's quality of life and creates a significant financial burden on the health care system. This retrospective study collected data from patients who received autologous MSCs injections of bone marrow aspirate concentrate (BMAC) and/or micro-fragmented adipose tissue (MFAT). Data from patient-reported outcomes (PROs) were collected pre-treatment and at post-treatment follow-ups and correspondences. Surveys distributed included Visual Analog Scale (VAS), Knee Injury and Osteoarthritis Outcome Score for Joint Replacement (KOOS, JR), and a patient satisfaction survey. Out of 151 patients that met clinical criteria, 103 patients (159 knees) had appropriate follow up data. Of the 103 patients, 25 patients had knee arthroscopy prior to stem cell injection. 63 patients received platelet-rich plasma (PRP) injections within 12 months and five patients had conversion to Total Knee Arthroplasty (TKA). BMAC, MFAT graft, and BMAC and MFAT graft groups showed significant improvement in both VAS and KOOS, JR between baseline and 3,6,12, and 24 months post-treatment (p<0.00001). Among BMAC only patients, KL grade breakdown showed significant improvement in VAS and KOOS, JR scores within 24 months post-treatment across all grades (2-4).

Keywords: Stem cells; Osteoarthritis; Bone marrow aspirate concentrate; Mesenchymal stem cells; Adipose-derived stem cells; Micro-fragmented adipose tissue; Autograft cells; Orthopedics.

Citation: Leung S, Khan A, Arias A, Hughes PE. The Effects of Autologous Stem Cells from Bone Marrow and Adipose Tissue on Patients with Knee Osteoarthritis. J Regen Biol Med. 2023;5(4):236-50.
DOI: https://doi.org/10.37191/Mapsci-2582-385X-5(4)-135

Abbreviations: VAS-Visual Analog Scale; KOOS-Knee injury and Osteoarthritis Outcome Score; JR-Joint Replacement; CI-Confidence Interval; KL-Kellgre-Lawrence classification system; BMAC-Bone Marrow Aspirate Concentrate.

Introduction

Osteoarthrtis (OA) is one of the most common causes of musculoskeletal pain, stiffness, and reduced function in the knee joint, limiting patients' ability to participate in daily activities [1]. Knee OA is a disorder resulting in structural and functional failure of the synovial joint, involving changes to the articular cartilage, subchondral bone, ligaments, and muscles [2]. Risk factors that can contribute to the onset of knee OA include age, sex, joint trauma, and obesity [3]. According to the Centers for Disease Control and Prevention (CDC), OA is a leading cause of disability in the United States with 23% of adults over the age of 18 years diagnosed with arthritis and a total annual medical cost of about $140 billion [4]. Current FDA approved treatments for knee OA include prescription medication, physical therapy, steroid or hyaluronic acid injections, knee arthroscopy, and total knee arthroplasty (TKA).

However, the long-term effects of these treatments fall short of the desired results of long-term pain relief without painful surgical procedures that place patients at risk of complications rendering due to invasiveness of the procedures. Current knee arthroscopy techniques for the knee may lead to only temporary relief and may accelerate the painful degenerative process of OA. Total knee arthroplasty can result in post-operative infection, blood clots or other medical complications due to the invasive nature of the procedure that requires hospitalization at significant costs. Current injection strategies focus on temporary relief without slowing the progression of the degenerative process [5,6]. Orthobiologic treatments with intra-articular injection of BMAC, PRP and MFAT grafts provides a novel treatment option for patients with knee OA that are non-invasive and potentially very effective in reducing pain long term. Existing published studies help provide support in stem cell therapy as a treatment method for degenerative knee OA [7-13].

Stem cell therapy has been gaining public interest as an alternative treatment for knee OA as opposed to surgical intervention. Currently, in the United States, studies are limited by FDA guidelines on treatment of all human cells, tissues, and cellular products. Allograft sources for mesenchymal stem cells MCSCs such as placenta and umbilical cord have become more popular in recent years due to the ease of treatment of injecting product straight from the bottle though the bioavailability of the cells have been questioned. Minimally manipulated products like autograft bone marrow aspirate (BMA), adipose tissue graft, and platelet-rich plasma (PRP) are not as tightly regulated or readily available but will not be rejected like an allograft may. Oliver, et al., evaluated the efficacy of bone marrow concentrate on knee osteoarthritis and found encouraging results indicating improvement in pain, functions, activities of daily living and quality of life on a six-month short-term scale [8].

PRP studies on knee OA treatment are becoming more prevalent as well. Numerous

Citation: Leung S, Khan A, Arias A, Hughes PE. The Effects of Autologous Stem Cells from Bone Marrow and Adipose Tissue on Patients with Knee Osteoarthritis. J Regen Biol Med. 2023;5(4):236-50.
DOI: https://doi.org/10.37191/Mapsci-2582-385X-5(4)-135

publications have shown PRP is clinically effective in reducing pain associated with knee OA. PRP is an autologous blood product that contains a high concentration of platelets (1 to 3 times greater than whole blood) which has been shown to alleviate pain and regulate inflammation [14]. A single injection of PRP is effective in improving symptoms associated with knee OA [15,16]. Studies have shown PRP injections compared to hyaluronic acid (HA) are more clinically effective in decreasing pain for up to 12 months [17]. PRP has also been shown to be clinically superior to cortisone injections [18].

BMAC has a rich source of mesenchymal stem cells (MSC). MSCs are pluripotent progenitor cells which have the capability to differentiate into various tissues including bone, fat, ligaments, tendons, and cartilage [19,20]. MSCs can be found in various tissues including bone marrow, adipose tissues, umbilical cord blood, muscle, dermis, periosteum, synovial membrane, synovial fluid, infrapatellar fat, bursa tissue, and articular cartilage [21].

Bone marrow does have a rich source of MSCs, however adipose tissue has been thought of as a good alternative source of MSCs as well due to its ease of accessibility. Investigation in BMAC and adipose tissues (MFAT) as treatment for knee OA has been increasing in recent years, but Mautner, et al., carried out a direct comparison between BMAC and adipose tissue. The outcome of BMAC versus adipose tissue injections in individuals with knee OA, found results displaying regardless of tissue source, both have significant improvements in pain and function from pre-procedure versus post-procedure [21]. Therefore, the purpose of this study is to expand the current data on BMAC and MFAT graft as a safe and effective treatment for patients with knee osteoarthritis in an outpatient office setting.

Materials and methods

Between December 2015 and February 2020, 151 patients with Knee OA were treated with either Bone Marrow Aspirate Concentrate (BMAC), adipose tissue (MFAT graft), or a combination of BMAC and MFAT graft injection. Clinical criteria were determined to be medically healthy patients (no history of cancer) suffering from knee pain of greater than 5 on the VAS with radiologic evidence of OA and knee cartilage wear with no significant deformity (less than 10 ° of knee varus or valgus deformity), no significant bone loss at joint, and patient not wishing to undergo knee arthroplasty. Pre-injection imaging (MRI and X-Ray) of 149 out of 159 treated knees were collected upon chart review. Kellgren-Lawrence (K-L) grading was determined and data collected from these patients were collected mostly retrospectively though some prospective data was obtained. Patients with known meniscal tears on MRI were encouraged to undergo knee arthroscopy to treat the meniscal pathology prior to BMAC or MFAT injection to their knee. Of the patients who underwent knee arthroscopy, the injection (BMAC and/or MFAT) was administered approximately 4-8 weeks post-operatively. PRP injections were administered to patients up to 3-12 months after the initial injection for a one-time biologic booster as needed for help to control knee pain. Patients were surveyed for pre injection and followed up 3 months, 6

Citation: Leung S, Khan A, Arias A, Hughes PE. The Effects of Autologous Stem Cells from Bone Marrow and Adipose Tissue on Patients with Knee Osteoarthritis. J Regen Biol Med. 2023;5(4):236-50.
DOI: https://doi.org/10.37191/Mapsci-2582-385X-5(4)-135

months, 12 months, and 24 months post BMAC and/or MFAT graft injection. Patients were asked to fill out patient reported outcome (PRO) surveys including the VAS, KOOS, JR, and patient satisfaction.

BMAC harvesting technique

The patient is placed in a lateral recumbent position. The bone marrow aspiration is harvested from the posterior superior iliac spine (PSIS) or iliac crest with an aspiration from a trocar and Jamshidi needle. Local anesthesia, 10mL of 1% Lidocaine HCl, is injected to the procedural site to anesthetize the patient's site of graft harvest. The procedural site is then sterilely prepared with Betadine swab sticks and draped with a sterile surgical drape. The two 30mL VacLok syringes as well as the trocar needle are coated with 8mL of the anticoagulant heparin. The bone marrow collection bag is injected with ACD-A (anticoagulant citrate dextrose solution, formula A) to prevent clotting. The system used for the initial patients was the Angel system from Arthrex for BMAC and researchers later converted to the Terumo Harvest BCT BMAC smart prep system.

A stab incision is made for the insertion of the trocar needle into the trochanter. Manual pressure is used to insert the trocar needle into the medullary cavity of the PSIS. Once the trocar needle is inserted into the posterior iliac crest, the driver and stylet are removed and replaced by the 30mL syringes one at a time to aspirate the bone marrow. The trocar needle is occasionally rotated 90 degrees during aspiration to change the angle of bone marrow collection. A total of 60mL of bone marrow is harvested and placed into the collection bag. The bone marrow aspirate (BMA) is filtered through a mesh filter into a 60mL syringe to remove bone fragments. The trocar needle is finally withdrawn, and pressure is immediately applied to the procedural site, followed by steri-strips and dressing application.

Filtered BMA is transferred to a process disposable container of the Terumo BCT Harvest BMAC kit to be a centrifuged with the Terumo Harvest system for 15 minutes separating red blood cells (RBCs), platelet-rich-plasma (PRP), and BMAC. The PRP from bone marrow is a platelet poor plasma (PPP) and should be described as coming from the bone marrow note the peripheral blood work PRP is harvested. PPP, platelet poor plasma, is first withdrawn to access the BMAC layer. Approximately 25cc of PPP and 12cc of BMAC is usually harvested from the 60cc of BMA. BMAC is transferred from the process disposable into a syringe and injected into the arthritic knee joint(s) under ultrasound guidance with a 22-gauge needle. The PPP is used as an initial injection to help in the accurate placement of the needle and injection of the BMAC and to the patient's knees with ultrasound guided injection. Patients were told not to use NSAIDs for 6 weeks after stem cell injection.

MFAT graft harvesting

Patients are placed in a lateral recumbent position. Local anesthesia, 20mL of 1% Lidocaine HCl with epinephrine, is injected into the procedural site in the lower flank to anesthetize the superficial fat layer under the skin. The procedural site is then sterilely prepared with betadine swab sticks and a sterile surgical drape. A stab incision is made

Citation: Leung S, Khan A, Arias A, Hughes PE. The Effects of Autologous Stem Cells from Bone Marrow and Adipose Tissue on Patients with Knee Osteoarthritis. J Regen Biol Med. 2023;5(4):236-50.
DOI: https://doi.org/10.37191/Mapsci-2582-385X-5(4)-135

at the trochanter, and adipose tissue is harvested from the trochanteric fat pad with suction applied with a syringe to a blunt-tip cannula, and the fat is collected into a 30mL VacLok syringe. The cannula is withdrawn, and pressure is applied to the procedure site, followed by steri-strips and dressing application.

Harvested adipose tissue is then placed into the Terumo Harvest system centrifuge for approximately 5 minutes to separate the oil layer, fat tissue and blood residues. The oil layer and blood residues were drawn out and discarded leaving behind the fat tissue. An emulsion is achieved mechanically using the micro-fragmented adipose tissue (MFAT) solution between two 1cc syringes and Luer-Lok connector to mobilize MSCs. The MFAT then transferred into 10mL syringes to be injected in the arthritic knee joint(s) under ultrasound guidance with an 18-gauge needle.

Results

A total of 151 patients met clinical criteria, with 103 patients (BMAC 77, MFAT graft 8, and BMAC and MFAT graft 18) and 159 knees (BMAC 121, MFAT graft 10, and BMAC & MFAT graft 28) having appropriate follow up data. The study group included 46 (44.7%) females and 57 (55.3%) males with an average age of 62 ± 13, ranging from 19 to 97 years. The average weight of patients was 187 ± 43 pounds.

Pre-injection imaging (MRI and X-Ray) of 149 out of 159 treated knees were collected upon chart review. Kellgren-Lawrence (K-L) grading was as follows: grade 0: 1(0.7%) knee, grade I: 1(0.7%) knee, grade II: 19(12.8%) knees, grade III: 96(64.4%) knees, and grade IV : 32(21.4%) knees.

Knee VAS pain scores during the subsequent follow ups demonstrated significant pain improvement pre-injection to post-injection 3,6,12, and 24 months (p<0.00001; Table 1).

The overall decrease for mean VAS pain score were 3.8, 3.7, 3.1, and 4.3 (mean=6.5, 2.7, 2.8, 3.4, and 2.2 at pre-injection and post-injection) respectively.

Figure 1: VAS reported retrospectively at pre-injection and 3, 6, 12 and 24 months. Visual Analog Scale reported retrospectively for patients who have received BMAC, MFAT, and BMAC and MFAT injections for outcomes at pre-injection and 3,6,12, and 24 months post-treatment.

Citation: Leung S, Khan A, Arias A, Hughes PE. The Effects of Autologous Stem Cells from Bone Marrow and Adipose Tissue on Patients with Knee Osteoarthritis. J Regen Biol Med. 2023;5(4):236-50.
DOI: https://doi.org/10.37191/Mapsci-2582-385X-5(4)-135

Pain/Functional Score	Pre-injection	3 Months	6 Months	12 Months	24 Months
VAS p-value (at 95% CI)	6.5 (± 2.5)	2.7 (± 2.3)<0.00001	2.8 (± 2.3)<0.00001	3.4 (± 2.7)<0.00001	2.2 (± 2.2)<0.00001
KOOS, JR (Interval Score) p-value (at 95% CI)	51.198 (± 16.793)	71.976 (± 16.630)<0.00001	75.537 (± 15.465)<0.00001	68.552 (± 20.510)<0.00001	76.187 (± 14.708)<0.00001

Table 1: Pain and functional results, pre-injection and post-injection 3, 6, 12, and 24 months. VAS and KOOS, JR scores reported by patients retrospectively for pre-injection and 3,6,12, and 24 months post-treatment. Results presented for all patients including BMAC, MFAT, and MFAT with BMAC recipients.

Figure 2: KOOS, JR reported retrospectively at pre-injection and 3, 6, 12 and 24 months. Knee Injury and Osteoarthritis Outcome Score reported retrospectively for patients who have received BMAC, MFAT, and BMAC and MFAT injections for outcomes at pre-injection and 3,6,12, and 24 months post-treatment.

VAS Score	Pre-injection	3 Months	6 Months	12 Months	24 Months
KL Grade 2 p value (at 95% CI)	4.9(± 2.4)	2.38(± 2.2)0.000895	1.4(± 1.3)<0.00001	3.1(± 2.4)0.016586	3.1(± 1.8)0.000659
KL Grade 3 p value (at 95% CI)	6.6(± 2.3)	3.0(± 2.6)<0.00001	3.0(± 2.3)<0.00001	2.8(± 2.1)<0.000011	2.5(± 2.6)<0.00001
KL Grade 4 p value (at 95% CI)	7.7(± 2.2)	3.2(± 2.3)0.013142	2.25(± 2.5)0.013797	2.7(± 2.2)0.004661	3.0(± 3.0)0.016877

Table 2: VAS Scores by Kellgren-Lawrence (KL) grade on X-Ray before treatment for BMAC only recipients. VAS scores by KL grade for Knee X-Rays obtained before treatment with outcomes reported by patients retrospectively for pre-injection and 3,6,12, and 24 months post-treatment. Results present only for BMAC recipients.

Citation: Leung S, Khan A, Arias A, Hughes PE. The Effects of Autologous Stem Cells from Bone Marrow and Adipose Tissue on Patients with Knee Osteoarthritis. J Regen Biol Med. 2023;5(4):236-50.
DOI: https://doi.org/10.37191/Mapsci-2582-385X-5(4)-135

Knee KOOS, JR scores showed overall significant functional improvements pre-injection to post-injection (p <0.00001; Table 1). The mean KOOS, JR pain and function score improvement was 20.957, 23.741, 17.396, 25.168 (mean=51.198, 71.976, 75.537, 68.552, and 76.187 at pre-injection and post-injection 3, 6, 12, 24 months). Figure 2 visualizes the progression of mean interval scores for KOOS, JR with a net increase (improvement) between 24 months post-treatment and baseline.

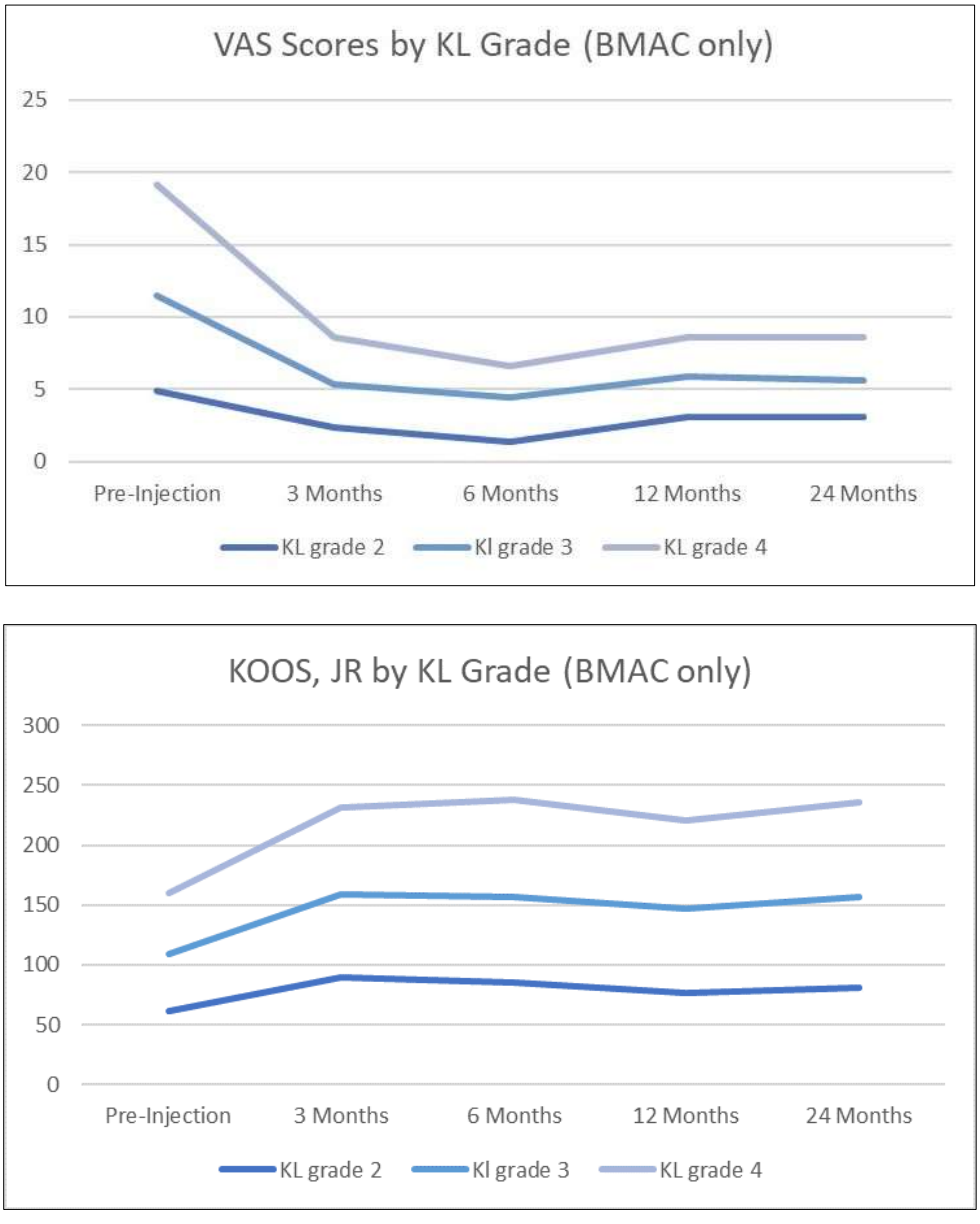

Figure 3: VAS and KOOS, JR pre-injection and 3,6,12 and 24 months by KL grade for BMAC-only recipients. Visual analog scale and Knee Injury Osteoarthritis Outcome Score were reported retrospectively for patients who only received BMAC injections for outcomes at pre-injection and 3,6,12, and 24 months post-treatment. Kellgren-Lawrence grade classification determined for treated knee(s) by X-ray before in-clinic treatment.

Citation: Leung S, Khan A, Arias A, Hughes PE. The Effects of Autologous Stem Cells from Bone Marrow and Adipose Tissue on Patients with Knee Osteoarthritis. J Regen Biol Med. 2023;5(4):236-50.
DOI: https://doi.org/10.37191/Mapsci-2582-385X-5(4)-135

KL-grade breakdown among BMAC patient reveals that across all KL grade classifications in the data, (KL grades 2, 3, and 4) patients had a significant improvement from baseline VAS scores and KOOS, JR between baseline and at a follow-up data point between 3- and 24-months post-treatment.

This breakdown suggests most significant improvement (p <0.00001) among KL grade 3 patients for both PROs. KL grade breakdown was not conducted for MFAT and BMAC and MFAT groups due to lack of data. Analysis with Pearson correlation revealed there is negligible correlation) with correlation coefficients of ≤ 0.03) between BMI and differences in pre-treatment and post-treatment VAS and KOOS scores for all aforementioned therapies. Furthermore, when data was divided by gender, the correlation between BMI and the outcome measures remained insignificant for both male and female groups.

Average patient satisfaction for stem cell injections was 7.7 out of 10, where 10 indicates extremely satisfied. 81% of patients would consider stem cell injections again (if needed) and 86% of patients would recommend stem cell injections to their family and friends.

KOOS, JR Score	Pre-injection	3 Months	6 Months	12 Months	24 Months
KL Grade 2 p-value (at 95% CI)	60.9 (± 16)	90(± 14.2) 0.001917	85.3 (± 19) 0.01337	76.7 (± 13.8) 0.001269	81.1(± 10.7)<0.00001
KL Grade 3 p-value (at 95% CI)	48.49 (± 15.3)	68.8(± 12.6)<0.00001	71.5(± 14.6)<0.00001	70.5(± 16.8)<0.00001	76(± 17.7)<0.00001
KL Grade 4 p-value (at 95% CI)	51(± 16)	72.3 (± 24.4) 0.281598*	81.3 (± 16.3) 0.051414*	73.8(±18.4) 0.001544	78.6(± 17.5) 0.000036

Table 3: (KOOS, JR) Scores by Kellgren-Lawrence (KL) grade on X-Ray before treatment for BMAC only recipients. KOOS, JR scores by KL grade for Knee X-Rays obtained before treatment with outcomes reported by patients retrospectively for pre-injection and 3,6,12, and 24 months post-treatment. Results present only for BMAC recipients.

Discussion

The purpose of this study was to examine the effects of autologous BMAC and Fat Graft on patients with knee osteoarthritis and pain in an outpatient office setting. Symptoms of knee OA affect the daily lives of millions of people, decreasing the quality of life.

The novel concept of stem cell therapy using intra-articular injection of MSCs has opened up another approach at treating knee OA. Currently more published studies are examining the viability and efficacy of BMAC and FAT Graft derived MSCs as a treatment method.

The data demonstrates that there are statistical improvements in pain and functions in treating knee OA with BMAC and/or FAT Graft performed in an outpatient office setting with a 2-year follow-up.

There were no complications or reactions to the procedures in this study and shows that harvesting of MSCs from bone marrow or adipose tissue and subsequent injections into the knee joint can be done safely in the

Citation: Leung S, Khan A, Arias A, Hughes PE. The Effects of Autologous Stem Cells from Bone Marrow and Adipose Tissue on Patients with Knee Osteoarthritis. J Regen Biol Med. 2023;5(4):236-50.
DOI: https://doi.org/10.37191/Mapsci-2582-385X-5(4)-135

medical office setting. Most of the patients received BMAC only treatment, with less receiving MFAT and even fewer receiving both injections on the same date.

When observing BMAC data by KL grade, all patients achieved on average statistically significant improvement of KOOS and VAS scores within 24 months of treatment, with best results seen among KL grade 2 and KL grade 3 patients, though this may be skewed due to not enough patients with KL grade 4 seen on X-ray.

Limitations of this study include a nonrandomized subject pool and a lack of a control group for analysis. With no control group or a randomization process, results cannot eliminate placebo effects or preexisting conditions of subjects that can influence their responses to BMAC and/or Fat graft.

The subjects of this study were patients who did not want invasive surgical procedures and wanted to try a stem cell procedure in its place. Additionally, BMAC and Fat graft samples were not sent for laboratory analysis for its cellular contents (MSCs, platelet, etc.). Due to this unknown, there is a possibility subjects were injected with less MSCs. But in some ways, it would be difficult to analyze the injection sample for the number of MCSs, as it would decrease the number of cells that were injected if a portion of the BMAC or MFAT grafts used in this study were sent for laboratory analysis, though this quality measure could ensure each patient is receiving a similar stimulus. To improve efficacy of treatment, future studies should focus on randomization and a control arm to eliminate bias and variability. There are many studies published in the literature that show the effectiveness of stem cell injections. But the question remains whether a placebo effect is possibly responsible for these results or the use of arthroscopic debridement with MSCs placement [12,13]. This current study has only one clinician obtaining the grafts and doing the injections for these patients which helps with standardization techniques for cell harvesting, processing, and delivery.

The biomechanics in which mesenchymal stem cells heal the knee joint has been looked at by many. MSCs secrete bioactive molecules that stimulate angiogenesis and tissue repair and reduce the response of T cells and inflammation. It appears that there is a potential triple effect from the bone marrow or fat graft injection to the knees. The triple effect describes the role the MCSs play in the healing and regeneration in the intraarticular cellular process includes: 1, the paracrine factor and anti-inflammatory effect, 2, influence in the local healing by the local tissue or cartilage cells, 3, the MCSs themselves differentiate to the tissue such as cartilage in the knee joint to heal/regenerate in areas of cartilage losses.

The cellular mediation and paracrine factor that occurs may include anti-inflammatory effect by the stem cells, with a release of exosomes and cytokines to has been suggested [24] if this is true that there are several mechanisms of healing and ways that the joint can heal for decreased pain will make this type of procedure revolution area in treating joint diseases.

Researcher may never completely understand the mechanism of the process involved in the healing of joints with mesenchymal stem cells

Citation: Leung S, Khan A, Arias A, Hughes PE. The Effects of Autologous Stem Cells from Bone Marrow and Adipose Tissue on Patients with Knee Osteoarthritis. J Regen Biol Med. 2023;5(4):236-50.
DOI: https://doi.org/10.37191/Mapsci-2582-385X-5(4)-135

from bone marrow or fat grafts but studies like this show that the injection of these autograft cells taken from individuals to heal their own joints such as the knee may be a relatively simple and noninvasive treatment.

Shapiro, et al., has demonstrated the safety and use of BMAC injection for the treatment of knee arthritis. And showed initial encouraging results with this treatment though it did show that the placebo had similar results. This brings into question whether the actual act of injection itself can influence the healing response in the knee joint [11].

In comparison to previous studies on mesenchymal stem cells, BMAC and MFAT injections for knee pain, this study is unique in that treatment was delivered in an office setting. Oliver, et al., have shown similar results as this current study for 2-year outcomes from mesenchymal stem cell autograft injections shelf pain score and functional score improvements. Sampson, et al., found 90% patient satisfaction with BMAC injection therapies [15].

Some studies emphasized the use of stem cells with surgical procedures to treat cartilage defects, as Kim, et al., has shown improvements in pain scores and functional outcomes at 12 months [7]. Kim suggests that the cutoff point for the use of mesenchymal stem cell autograft should be 60 years old in their study looking at isolated cartilage lesions in the knee. The researcher was using surgical intervention with arthroscopy treating his patients. Finding that lesion size also influences the final results. With larger than $6cm^2$ lesions having fewer effective outcomes. It has been well known in surgery orthopedic literature that older patients with arthritic lesions tend to not do well with arthroscopic procedures anyway. It could be that this could be the problem with the stem cell treatments for older patients. In this study the researchers have used the office setting for the procedure with minimal trauma from graft harvest and injections into knee joints. Like Oliver, et al., researchers have found good to excellent results occurring with the injections of BMAC and MFAT at 85% [25].

The fact that microfracture surgeries in knees tend to produce results that degenerate with time [26] and Microfracture procedures of the knee produce a scar type I cartilage in the cartilage defect compared to the normal hyaline type II cartilage may be the fact of the decreased number of mesenchymal stem cells that are present after microfracture in the cartilage lesion were as the use of autograft mesenchymal stem cell grafts from the BMAC and MFAT may increase the number of cells and allow hilum-like cartilage to be formed in the joint. Improving the clinical results of a microfracture procedure or any cartilage regeneration procedure may lie in improving the biologic effects at the cellular level with certain additives of cytokines, MSCs or other cellular modulators to create an environment more conducive to producing a hyaline type II cartilage. Determining the optimal dose of mesenchymal stem cells either from bone marrow or fat has yet to be developed nor has the techniques mastered in order of injections and possible additive growth factors to enhance cellular healing of the joint needs to be investigated further. The role of PRP or other growth factors as a "booster" to the cellular effect of the MSCs has been proposed

Citation: Leung S, Khan A, Arias A, Hughes PE. The Effects of Autologous Stem Cells from Bone Marrow and Adipose Tissue on Patients with Knee Osteoarthritis. J Regen Biol Med. 2023;5(4):236-50.
DOI: https://doi.org/10.37191/Mapsci-2582-385X-5(4)-135

here as has been proposed by other authors to help increase the cellular effect of the mesenchymal stem cell particularly in different differentiating into chondrocytes or other cellular lines that will help heal a degenerative joint [13]. The possible use of biologic scaffolds has been proposed to help in the healing of knee joint chondral defects. The future may entail a multi-disciplinary approach in which arthroscopic surgery followed by stem cells followed by PRP followed by any sort of oral supplement or IV supplement may be used to create an optimal environment for joint healing of not only the knee but other loading joints of the body. Obviously more research needs to be done in these areas and is being done.

The advantage of this process of injection of the BMAC or MFAT to multiple joints is obvious. The fact that researchers can inject multiple joints and in one office setting within reason could provide a huge benefit to patients who suffer from multiple joint pains particularly from either cartilage degeneration, tendon tears or ligament injuries. This may be the true and spectacular benefit of stem cells in the future for the treatment in 1 setting of multiple joint problems. Sampson, et al., found that the knee joint responded better than other joints in the body to bone marrow (BMAC) therapy injections and that the weight of the patient and the BMI may influence the outcome [15].

The conclusion of this study shows that injections with adults' mesenchymal stem cells can decrease knee pain and increase overall activity levels for patients with knee pain with two years of follow up. Though this was not a randomized double-blind study it does show that cellular based orthobiologic therapy can improve pain scores and activity scores. The principal reason for treatment by cellular therapy is to lower pain and increase daily function which can help avoid surgical interventions, something that patients are most interested in. Especially in this post pandemic period, patients are increasingly worried about infection rates and exposure to disease in hospitals.

The study shows that mesenchymal stem cells from the bone marrow aspirate concentrate and micronized adipose tissue is a viable source of pain relief for patients. Mesenchymal stem cell (MSC) therapy from autograft adult stem, BMAC or MFAT, have shown to be successful. Currently, no studies suggest a statistical difference between MFAT and BMAC outcomes for treatment of symptomatic knee osteoarthritis. Studies thus far indicate similar significant improvement of symptoms by both treatments [9]. Future studies are needed to compare MFAT and BMAC treatment results in patients with knee pathology and pain.

Other studies have shown that allograft fetal tissue injections from Wharton's jelly or amniotic membrane tissue have improved knee pain [27-29]. In the clinic researchers have tried these allograft orthobiologic injections but have not shown anywhere near the success that researchers have seen with MFAT or BMAC. Results in the clinic have been poor for patients given dehydrated amniotic membrane or fetal cells sources such as Wharton's jelly. The patient population is not interested in a placebo but are interested in therapies that are alternatives to surgeries.

Citation: Leung S, Khan A, Arias A, Hughes PE. The Effects of Autologous Stem Cells from Bone Marrow and Adipose Tissue on Patients with Knee Osteoarthritis. J Regen Biol Med. 2023;5(4):236-50.
DOI: https://doi.org/10.37191/Mapsci-2582-385X-5(4)-135

Thus, the researchers have not used or compared a non-treated population of patients to those patients treated with orthobiologics (MFAT or BMAC). Further studies need to be done head-to-head comparing autograft vs allograft orthobiologics to help practitioners choose the treatment that can improve pain scores and function scores on a consistent basis.

There are also ethical concerns regarding use of fetal tissue. Under past administrations, restrictions have been placed on FDA activity for supply of allograft fetal tissue due to pressure from anti-abortion groups and stakeholders [30]. The reasons that autograft tissue might provide better results is that there is no rejection of tissue and the cell viability may be higher when compared to allograft tissue. The cellular function with production of cytokines or other growth factors present in the bone marrow autografts and adipose tissue autografts may produce the difference in superior results compared to allografts. Longer term studies are needed for a thorough comparison of autologous bone marrow derived versus umbilical cord derived mesenchymal cell therapy with appropriate breakdown of outcomes by patient BMI, KL grade, and with a larger patient population. Studies need to be done to look at the *in vivo* function of the MSCs and how they are incorporated in the tissue and how they may decrease pain in the tissue.

The ideal orthobiologic injection would improve pain scores and function scores by production of anti-inflammatory factors such as alpha-2-macroglobulin and other cytokines that can affect local joints and can provide cellular modulation. In conclusion, researchers hope the study will become part of the record of orthobiologic treatments with BMAC or MFAT. The study has a significant number of patients that were injected with both knees and a shoulder or other joint as part of the treatment. Most patients received at least 1/3 of the stem cells injected into each knee and another joint. Staging later platelet rich plasma (PRP) injections into both patient populations of micronize fat or bone marrow aspirate concentrate BMAC was done consistently. Researchers would also add a PRP injection at about 4-8 weeks post-injection for patients that had not improved noticeably. One of the advantages of the BMAC procedure is the ability to inject the by-product from the Harvest BMAC kit of platelet poor plasma (PPP) into multiple joints that are painful. This is not seen with micronized fat tissue as it does not give a plasma to be injected that time. The population was not interested in having a randomized trial. The patients were interested in getting stem cell treatments for the pain. The study is a follow-up of the success rate of these patients that chose this process.

Most of these patients had already had cortisone injections or hyaluronic acid injections. Some had undergone knee arthroscopy with minimal to no relief while others had a knee replacement on one side and were not interested in doing this on the contralateral side. Also, the enticement was the possibility of injecting other joints most commonly the shoulder or elbow with the stem cell therapy at the same sitting.

Second look arthroscopy from other studies have shown the increased healing present in

Citation: Leung S, Khan A, Arias A, Hughes PE. The Effects of Autologous Stem Cells from Bone Marrow and Adipose Tissue on Patients with Knee Osteoarthritis. J Regen Biol Med. 2023;5(4):236-50.
DOI: https://doi.org/10.37191/Mapsci-2582-385X-5(4)-135

the joints particularly and for cartilage defects. Though the researchers did not assess or reference knee alignment in the study, the point was to look at all comers for who are interested in trying this new biologic therapy for knee pain. All interviews and data collection were done by the research assistant by communication via email, phone and personal interview or mail correspondence. Obviously there needs to be more studies or case review reports on the success of stem mesenchymal stem cells for the treatment of knee pain and osteoarthritis. A few of the patients did have second look arthroscopy as the patients did show vascularization healing of cartilage lesions. Some patients had MRI follow ups but researchers did not have specific volume assessments of these MRIs. A strength of this study is the large number of patients that were treated. Another strength of this study was all the procedures were performed by the same physician and were completed in a clinic office setting without the need for general anesthesia with only local anesthetic used for pain control. A weakness of this study is the lack of randomization with patients self-choosing for treatment with autologous MSCs. Patients were discouraged from using the anti-inflammatory medications to avoid the impact on post injection cellular activity for 6 weeks after initial knee injection and also to avoid any active impaction activities that cause irritation in the joint such as running and jumping. Follow up was performed as described with interviews done and data collected by a research assistant, not by the clinician providing the care. Only one Orthopedic surgeon was involved in all the clinical applications and treatments of harvesting and injecting the MSCs from BMAC or MFAT. The researchers hope that the study will contribute to the use of adult mesenchymal stem cells (MSCs) for healing and pain relief of pathologic joints and soft tissues. The researchers believe that future studies will show this treatment option of MSCs is a viable option to treat painful knees and most patient populations interested in avoiding surgical intervention.

Conclusion

This study follows knee osteoarthritic patients with pain who have undergone the novel stem cell therapy of intra-articular injection of BMAC and/or MFAT graft in an outpatient office setting. There were no complications in the harvest and injection therapy in this study. Based on the data, BMAC and MFAT grafts performed in an office setting showed significant results in improving pain and functionality. Although this treatment method is not yet FDA approved, the favorable outcomes show BMAC and MFAT graft as an excellent alternative to knee arthroplasty without the downtime that is associated with a surgical procedure in the operative room and hospitalization. While this study adds to evidence of BMAC and MFAT as a treatment option for knee OA, further studies are essential in basic science and clinical studies to show not only the effectiveness but also to explain any mechanism of action that MSCs have and what other growth factors or supplements can enhance joint healing.

The addition of randomized controls and a longer follow-up period would also be beneficial for understanding the roles of MSCs use for joint pain.

Citation: Leung S, Khan A, Arias A, Hughes PE. The Effects of Autologous Stem Cells from Bone Marrow and Adipose Tissue on Patients with Knee Osteoarthritis. J Regen Biol Med. 2023;5(4):236-50.
DOI: https://doi.org/10.37191/Mapsci-2582-385X-5(4)-135

References

1. Hunter DJ, McDougall JJ, Keefe FJ. The Symptoms of Osteoarthritis and the Genesis of Pain. Rheum Dis Clin North Am. 2008;34(3):623-43. PubMed | CrossRef
2. Fu K, Robbins SR, McDougall JJ. Osteoarthritis: The Genesis of Pain. Rheumatology (Oxford). 2018;57(4):43-50. PubMed | CrossRef
3. Neogi T, Zhang Y. Epidemiology of Osteoarthritis. Rheum Dis Clin North Am. 2013;39(1):1-19. PubMed | CrossRef
4. Barbour KE, Helmick CG, Boring M, Brady TJ. Vital Signs: Prevalence of Doctor-Diagnosed Arthritis and Arthritis-Attributable Activity Limitation-United States, 2013-2015. MMWR Morb Mortal Wkly Rep. 2017;66(9):246-53. PubMed | CrossRef
5. Hootman JM, Helmick CG, Barbour KE, Theis KA, Boring MA. Updated Projected Prevalence of Self-Reported Doctor-Diagnosed Arthritis and Arthritis-Attributable Activity Limitation Among US Adults, 2015-2040. Arthritis Rheumatol. 2016;68(7):1582-7. PubMed | CrossRef
6. Murphy LB, Cisternas MG, Pasta DJ, Helmick CG, Yelin EH. Medical Expenditures and Earnings Losses Among US Adults with Arthritis in 2013. Arthritis Care Res (Hoboken). 2018;70(6):869-76. PubMed | CrossRef
7. Kim JD, Lee GW, Jung GH, Kim CK, Kim T, Park JH, et al. Clinical Outcome of Autologous Bone Marrow Aspirates Concentrate (BMAC) Injection in Degenerative Arthritis of the Knee. Eur J Orthop Surg Traumatol. 2014;24(8):1505-11. PubMed | CrossRef
8. Ng J, Little CB, Woods S, Whittle S, Lee FY, Gronthos S, et al. Stem Cell-Directed Therapies for Osteoarthritis: The Promise and the Practice. Stem Cells. 2020;38(4):477-86. PubMed | CrossRef
9. Mautner K, Bowers R, Easley K, Fausel Z, Robinson R. Functional Outcomes Following Microfragmented Adipose Tissue Versus Bone Marrow Aspirate Concentrate Injections for Symptomatic Knee Osteoarthritis. Stem Cells Transl Med. 2019;8(11):1149-1156. PubMed | CrossRef
10. Oliver KS, Bayes M, Crane D, Pathikonda C. Clinical Outcome of Bone Marrow Concentrate in Knee Osteoarthritis. J Prolotherapy. 2015;7:937-46.
11. Shapiro SA, Kazmerchak SE, Heckman MG, Zubair AC, O'Connor MI. A Prospective, Single-Blind, Placebo-Controlled Trial of Bone Marrow Aspirate Concentrate for Knee Osteoarthritis. Am J Sports Med. 2017;45(1):82-90. PubMed | CrossRef
12. Chahla J, Piuzzi NS, Mitchell JJ, Dean CS, Pascual-Garrido C, LaPrade RF, et al. Intra-Articular Cellular Therapy for Osteoarthritis and Focal Cartilage Defects of the Knee: A Systematic Review of the Literature and Study Quality Analysis. J Bone Joint Surg Am. 2016;98(18):1511-21. PubMed | CrossRef
13. Cui GH, Wang YY, Li CJ, Shi CH, Wang WS. Efficacy of Mesenchymal Stem Cells in Treating Patients with Osteoarthritis of the Knee: A Meta-Analysis. Exp Ther Med. 2016;12(5):3390-3400. PubMed | CrossRef
14. Centeno C, Pitts J, Al-Sayegh H, Freeman M. Efficacy of Autologous Bone Marrow Concentrate for Knee Osteoarthritis with and without Adipose Graft. Biomed Res Int. 2014;2014:370621. PubMed | CrossRef
15. Sampson S, Smith J, Vincent H, Aufiero D, Zall M, Botto van Bemden A. Intra-Articular Bone Marrow Concentrate Injection Protocol: Short-Term Efficacy in Osteoarthritis. Regen Med. 2016;11(6):511-20. PubMed | CrossRef
16. Cook CS, Smith PA. Clinical Update: Why PRP Should be Your First Choice for Injection Therapy in Treating Osteoarthritis of the Knee. Curr Rev Musculoskelet Med. 2018;11(4):583-92. PubMed | CrossRef
17. Glynn LG, Mustafa A, Casey M, Krawczyk J, Blom J, Galvin R, et al. Platelet-Rich Plasma (PRP) Therapy for Knee Arthritis: A Feasibility Study in Primary Care. Pilot Feasibility Stud. 2018;4:93. PubMed | CrossRef
18. Patel S, Dhillon MS, Aggarwal S, Marwaha N, Jain A. Treatment with Platelet-Rich Plasma is More Effective than Placebo for Knee Osteoarthritis: A Prospective, Double-Blind, Randomized Trial. Am J Sports Med. 2013;41(2):356-64. PubMed | CrossRef
19. Cerza F, Carnì S, Carcangiu A, Di Vavo I, Schiavilla V, Pecora A, et al. Comparison between Hyaluronic Acid and Platelet-Rich Plasma, Intra-Articular Infiltration in the Treatment of Gonarthrosis. Am J Sports Med. 2012;40(12):2822-7. PubMed | CrossRef

Citation: Leung S, Khan A, Arias A, Hughes PE. The Effects of Autologous Stem Cells from Bone Marrow and Adipose Tissue on Patients with Knee Osteoarthritis. J Regen Biol Med. 2023;5(4):236-50.
DOI: https://doi.org/10.37191/Mapsci-2582-385X-5(4)-135

20. Migliorini F, Driessen A, Quack V, Sippel N, Cooper B, Mansy YE, et al. Comparison between Intra-Articular Infiltrations of Placebo, Steroids, Hyaluronic and PRP for Knee Osteoarthritis: A Bayesian Network Meta-Analysis. Arch Orthop Trauma Surg. 2021;141(9):1473-1490. PubMed | CrossRef
21. Caplan AI, Dennis JE. Mesenchymal Stem Cells as Trophic Mediators. J Cell Biochem. 2006;98(5):1076-84. PubMed | CrossRef
22. Fortier LA, Potter HG, Rickey EJ, Schnabel LV, Foo LF, Chong LR, et al. Concentrated Bone Marrow Aspirate Improves Full-Thickness Cartilage Repair Compared with Microfracture in the Equine Model. J Bone Joint Surg Am. 2010;92(10):1927-37. PubMed | CrossRef
23. Lodi D, Iannitti T, Palmieri B. Stem Cells in Clinical Practice: Applications and Warnings. J Exp Clin Cancer Res. 2011;30(1):9. PubMed | CrossRef
24. Jeyaraman M, Muthu S, Gulati A, Jeyaraman N, G S P, Jain R. Mesenchymal Stem Cell Derived Exosomes: A Potential Therapeutic Avenue in Knee Osteoarthritis. Cartilage. 2021;13(1):1572-85. PubMed | CrossRef
25. Kim YS, Choi YJ, Koh YG. Mesenchymal Stem Cell Implantation in Knee Osteoarthritis: An Assessment of the Factors Influencing Clinical Outcomes. Am J Sports Med. 2015;43(9):2293-301. PubMed | CrossRef
26. Goyal D, Keyhani S, Lee EH, Hui JH. Evidence-Based Status of Microfracture Technique: A Systematic Review of Level I And II Studies. Arthroscopy. 2013;29(9):1579-88. PubMed | CrossRef
27. Günay AE, Karaman I, Guney A, Karaman ZF, Demirpolat E, Gonen ZB, et al. Assessment of Clinical, Biochemical, and Radiological Outcomes Following Intra-Articular Injection of Wharton Jelly Derived Mesenchymal Stromal Cells in Patients with Knee Osteoarthritis: A Prospective Clinical Study. Medicine (Baltimore). 2022;101(37):e30628. PubMed | CrossRef
28. Ryu DJ, Jeon YS, Park JS, Bae GC, Kim JS, Kim MK. Comparison of Bone Marrow Aspirate Concentrate and Allogenic Human Umbilical Cord Blood Derived Mesenchymal Stem Cell Implantation on Chondral Defect of Knee: Assessment of Clinical and Magnetic Resonance Imaging Outcomes at 2-Year Follow-Up. Cell Transplant. 2020;29:963689720943581. PubMed | CrossRef
29. Wang L, Tran I, Seshareddy K, Weiss ML, Detamore MS. A Comparison of Human Bone Marrow Derived Mesenchymal Stem Cells and Human Umbilical Cord Derived Mesenchymal Stromal Cells for Cartilage Tissue Engineering. Tissue Eng Part A. 2009;15(8):2259-66. PubMed | CrossRef
30. Wadman M. Trump administration to review human fetal tissue research. Science insider. 2018.

Citation: Leung S, Khan A, Arias A, Hughes PE. The Effects of Autologous Stem Cells from Bone Marrow and Adipose Tissue on Patients with Knee Osteoarthritis. J Regen Biol Med. 2023;5(4):236-50.
DOI: https://doi.org/10.37191/Mapsci-2582-385X-5(4)-135