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Mesenchymal Stem Cell Therapy in Osteoarthritis Patients: A Two-Year Prospective Evaluation of Knee Joint Function

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ABSTRACT

This study evaluated the functional effects of stem cell therapy on the knees of osteoarthritis patients (OP) with at 1, 2 months, and 2-year follow-up intervals. Initially, 25 patients were enrolled, but data from only 15 patients were available at the end of the two-year follow-up (approximately 40% loss to follow-up). Significant improvements in the range of motion (ROM) were observed during the early post-treatment period (1st and 2nd months). However, a slight decline in ROM was noted at the 2-year mark, which was not statistically significant in the dominant knee ($p=0.06$). In contrast, the non-dominant knee showed a statistically significant deterioration over the same period ($p=0.04$). Visual Analog Scale (VAS) scores for pain and fatigue demonstrated marked improvement in the early period post-treatment, but by the end of two years, pain had partially increased and fatigue had significantly worsened. Functional tests such as the 30-second sit-to-stand and walking distance tests showed early improvements post-treatment; however, a declining trend was observed at the two-year follow-up. Berg balance scale improved following therapy and this improvement was largely maintained at the end of two years. Western Ontario and McMaster Universities Arthritis Index (WOMAC) scores indicated significant early improvements, and although they worsened by the end of two years, they remained significantly better than baseline. Subjective assessments revealed that patients who adhered to regular exercise achieved better clinical outcomes, while those who did not exercise reported increased pain and functional decline. Patients who did not respond to treatment underwent either knee arthroplasty or repeat stem cell therapy. Overall, stem cell therapy provided significant early clinical and functional improvements in osteoarthritic knees; however, a reduction in efficacy was observed in the long term, with deterioration noted in some parameters.

Introduction

Osteoarthritis (OA) is one of the most prevalent degenerative joint disorders globally, particularly affecting the aging population. Characterized by the progressive breakdown of articular cartilage, subchondral bone remodeling, and synovial inflammation, OA leads to chronic pain, joint stiffness, reduced mobility, and a considerable decline in quality of life. With the global increase in life expectancy, the burden of OA is expected to rise substantially, placing an increasing strain on healthcare systems and societal productivity.

The pathogenesis of OA is complex and multifactorial. While mechanical stress due to joint overuse or injury is a key contributor, growing evidence highlights the role of chronic low-grade inflammation, oxidative stress, and metabolic dysfunction in the progression of the disease. These factors collectively alter the joint microenvironment, contributing to cartilage degradation and impaired tissue repair. Despite the availability of various treatment modalities,including pharmacological agents such as non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids, as well as non-pharmacologic approaches like physical therapy and lifestyle modification,current therapies primarily offer symptomatic relief rather than addressing the underlying pathology. Moreover, they lack the ability to halt or reverse structural damage, underscoring the need for innovative therapeutic strategies with regenerative potential[1].

In recent years, regenerative medicine has emerged as a promising frontier for OA management, particularly with the advent of cell-based therapies. Among these, mesenchymal stem cells (MSCs) have attracted considerable attention due to their multipotent differentiation capacity and immunomodulatory properties. MSCs can differentiate into chondrogenic, osteogenic, and adipogenic lineages, making them suitable for repairing joint tissues[2]. Initially derived from bone marrow (BM-MSCs), MSCs have since been successfully isolated from a variety of other tissues, including adipose tissue (AD-MSCs), umbilical cord (UC-MSCs), and amniotic fluid[2]. These cells exert their therapeutic effects not only through direct differentiation but also by secreting bioactive molecules that modulate immune responses, inhibit inflammation, and promote tissue regeneration[1].

Importantly, the biological behavior of MSCs varies depending on their tissue source. For example, UC-MSCs are known for their higher proliferative potential and enriched cytokine secretion profile, while AD-MSCs are recognized for their robust immunosuppressive capabilities[1], [3]. Clinical studies have shown that intra-articular injection of BM-MSCs can lead to cartilage regeneration, pain reduction, and improved joint function in OA patients[4-7]. Similarly, therapies employing AD-MSCs and UC-MSCs have also demonstrated favorable safety profiles and positive clinical outcomes [8-13]. However, the therapeutic success of MSC-based treatments is influenced by several variables, including the origin of the cells, culture protocols, administration route, dosage, and timing[4,9,11].

One major limitation in MSC-based therapies is the gradual decline in their proliferative and differentiation capacities during in vitro expansion, which may result in insufficient cell numbers for clinical use[11]. To address this challenge, various preconditioning strategies have been explored to enhance MSC efficacy. Among them, low-level laser therapy (LLLT) has emerged as a non-invasive technique that may stimulate MSC activity by increasing ATP production, enhancing cell viability, and upregulating the expression of regenerative growth factors[15-21]. These effects suggest that LLLT could potentiate the therapeutic action of MSCs, particularly in the context of tissue regeneration for OA.

Although previous meta-analyses have concluded that MSCs are effective in reducing OA-associated pain and improving joint function[22-24] many of these studies are constrained by methodological limitations. These include small sample sizes, heterogeneous patient populations, and the use of combination treatments, which confound the interpretation of MSCs' standalone efficacy. For example, Song et al[23] included a mix of randomized controlled trials, cohort studies, and retrospective analyses, resulting in a lower overall level of clinical evidence. Other meta-analyses incorporated concurrent interventions such as platelet-rich plasma, bone marrow concentrate, or surgical procedures like microfracture and high tibial osteotomy[22,24]. These confounding factors make it difficult to assess the true regenerative impact of MSCs when used alone.

Given these considerations, the present study aims to evaluate the long-term effects of isolated MSC injections on functional recovery in OA patients, building on the findings from our previous work[25]. Patients were assessed using a combination of subjective measures and objective physical performance tests before treatment, at 2–3 months post-treatment, and again two years later. The primary objective was to determine the sustained therapeutic efficacy of MSC therapy on knee function, thereby providing a clearer understanding of its standalone regenerative potential.

Methods

STUDY DESIGN AND PROCEDURE

This retrospective study included patients who presented to the Orthopedics and Physical Therapy outpatient clinics

at Balıkesir State Hospital between September 21, 2020, and February 9, 2022. The current mean age of the patient group was over 65 years, and their body mass index (BMI) was ≥30. Patients diagnosed with osteoarthritis (OA) and who voluntarily received mesenchymal stem cell (MSC) therapy were included in the study. Inclusion criteria consisted of confirmed OA diagnosis by a specialist physician, presence of knee pain and restricted joint mobility, and having undergone MSC therapy. Exclusion criteria were a diagnosis of dementia, inability to participate in regular follow-ups, or interruption of treatment due to other comorbid conditions.

Available medical records included pre-treatment evaluations as well as assessments at the 1st and 2nd months following the procedure. Assessments were carried out using the Knee Evaluation Form, Berg Balance Scale, Timed Up and Go (TUG) test, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and the Visual Analog Scale (VAS) for pain. Additionally, scores from the 6-Minute Walk Test were recorded. These short-term (3-month) results of MSC therapy were previously published and reported positive outcomes[25].

As a continuation of that study, the same patients were contacted by phone two years after the initial treatment. Of the original 25 participants, only 15 were successfully reached for follow-up: five patients had died and three could not be contacted. Re-evaluations were conducted using the same tools: VAS for pain, range of motion (extension and flexion), sit-to-stand test, walking performance, WOMAC scores, and Berg Balance Scale.

Furthermore, patients were asked subjective questions regarding the impact of knee pain on their daily lives, their compliance with regular exercise, difficulties in daily activities, and whether they had undergone any alternative treatments or surgical interventions during the two-year period.

MSC THERAPY PROTOCOL AND PATIENTS

Patients were diagnosed with knee osteoarthritis based on the clinical and radiographic criteria established by the American College of Rheumatology (ACR). The diagnosis required the presence of knee pain along with at least three of the following: age >50 years, morning stiffness lasting <30 minutes, crepitus on active motion, bony tenderness, bony enlargement, and no palpable warmth. Radiographic evidence was confirmed using the Kellgren-Lawrence grading scale, with included patients having grade II or III OA.

The MSC therapy was performed using MilliGraft, a single-use, semi-sterile and sterile medical device employing SELF-FAT technology. This closed-system device allows for minimal manipulation and purifies adipose tissue in a single surgical step to produce a homogeneous fraction rich in MSCs. Adipose tissue was harvested from the lower abdominal region in all patients under local anesthesia. This site was chosen for its accessibility, minimal discomfort, and consistent fat yield. Standardized liposuction procedures were used to ensure uniformity in sample collection. During preparation, 10–20 cc of adipose tissue was harvested and homogenized. For each 5 cc of adipose tissue, 2–2.5 cc of physiological saline and lactated Ringer's solution was added. The tissue was then filtered to yield 8–9 cc of purified adipose tissue enriched with mesenchymal stem cells from every 10 cc of raw fat. The resulting MSC-rich adipose product was then injected into the target site. The entire procedure lasted approximately 30–40 minutes.

STATISTICAL ANALYSIS

Data analysis was performed using IBM SPSS Statistics software, version 25.0. The normality of continuous variables was assessed using the Shapiro-Wilk test. For normally distributed parameters, repeated measures within groups were analyzed using Repeated Measures Analysis of Variance (ANOVA). Bonferroni correction was applied in post-hoc analyses to determine the specific time points between which significant differences occurred. For variables that did not follow a normal distribution, appropriate non-parametric tests were used. Results were expressed as mean ± standard deviation (SD), and $p<0.05$ was considered statistically significant.

Results

This study evaluated the functional outcomes of mesenchymal stem cell (MSC) therapy in patients with knee osteoarthritis at 1 and 2 months post-treatment, as well as at the 2-year follow-up. Of the initial 25 participants, follow-up data at 2 years were available for only 15 patients. Five patients had died, and three could not be contacted, resulting in a 40% attrition rate. Complete datasets were obtained from 15 of the remaining 17 patients, highlighting the challenges of long-term follow-up in chronic conditions.

RANGE OF MOTION (ROM)

Assessment of joint ROM (Table 1) showed significant improvement in the dominant knee at both 1 and 2 months following treatment (1–2 months: $p = 0.004$; 1–3 months: $p = 0.000$). A mild decline was observed at the 2-year follow-up, though this change did not reach statistical significance ($p = 0.06$). The non-dominant knee also demonstrated significant early improvements ($p < 0.01$); however, values declined below baseline at 2 years, indicating functional deterioration ($p = 0.04$).

PAIN AND FATIGUE (VAS SCORES)

Pain levels, assessed by the Visual Analog Scale (VAS), significantly decreased during the early period (1–2 months: $p = 0.002$; 1–3 months: $p = 0.000$). However, at the 2-year follow-up, pain had increased and approached pre-treatment levels ($p = 0.227$). Fatigue scores similarly improved in the early period ($p < 0.01$) but showed a statistically significant increase at 2 years compared to baseline ($p = 0.01$).

FUNCTIONAL PERFORMANCE TESTS

The 30-second sit-to-stand test revealed significant early improvements ($p < 0.01$), followed by a decline at 2 years that approached statistical significance ($p = 0.09$). Walking performance, as measured by the 6-minute walk test, improved significantly post-treatment with average distances reaching approximately 440 meters. However, by year two, distances regressed toward baseline values ($p = 0.001$ and $p = 0.03$).

BALANCE AND OVERALL FUNCTION

The Berg Balance Scale demonstrated significant improvements at 1 and 2 months ($p < 0.001$), which were largely maintained at the 2-year follow-up ($p = 0.005$). WOMAC scores—reflecting pain, stiffness, and physical function—also improved significantly in the early stages ($p < 0.005$). Although scores worsened slightly by the 2-year follow-up, they remained significantly better than baseline ($p = 0.01$).

SUBJECTIVE FINDINGS AND INDIVIDUAL VARIABILITY

Among the 15 patients assessed, 5 reported no or low pain (VAS ≤ 5), while 10 reported high pain levels (VAS ≥ 7). Notably, patients who did not engage in regular exercise tended to report earlier recurrence of pain. Knee flexion was generally preserved (100°–135°), though two patients demonstrated decreased flexion (90°–100°). Knee extension was maintained at 165°–180° in all patients, indicating preserved passive ROM.

WALKING PERFORMANCE

Walking capacity varied across patients. Four were able to walk more than 500 meters, representing a high functional level. In contrast, five patients walked less than 200 meters, indicating significant functional limitations. One obese patient could walk only 10 meters.

WOMAC FUNCTIONAL SCORES

On the WOMAC scale (0–100, with higher scores indicating worse function), seven patients scored ≤50, suggesting good functional benefit from the treatment. Conversely, six patients scored ≥80, indicating poor or inadequate response.

IMPACT OF EXERCISE AND ADDITIONAL INTERVENTIONS

Patients who continued exercise reported better outcomes. Five exercised regularly and described themselves as being in "very good condition," characterized by low pain, good ROM, and high walking performance. In contrast, six non-exercising patients reported recurrence of pain.

SURGICAL AND ADDITIONAL TREATMENTS

Two patients underwent total knee arthroplasty following MSC therapy, suggesting insufficient therapeutic response. Additionally, two patients received a second round of MSC therapy, possibly indicating limited effectiveness of the initial application.

Discussion

In this study, the clinical and functional effects of mesenchymal stem cell (MSC) therapy in patients with knee osteoarthritis (OA) were evaluated at 1 and 2 months, and again at a 2-year follow-up. A notable loss to follow-up of 40% over the long-term highlights the challenges of conducting extended studies in chronic conditions. This limitation is frequently reported in the literature and underscores the difficulties in assessing long-term treatment efficacy[26,27].

Assessments of range of motion (ROM) showed significant improvements in both dominant and non-dominant knees during the early post-treatment period (1st and 2nd months). However, at the 2-year mark, a statistically significant decline in ROM was observed in the non-dominant knee, whereas the dominant knee showed a slight, non-significant regression. These findings suggest that while MSC therapy may offer early functional benefits, the sustainability of cartilage regeneration may be limited due to progressive joint degeneration over time[28,29].

Pain scores (VAS) also showed a marked reduction during the early post-treatment period, but by two years, pain levels had gradually increased and approached pre-treatment values. Similarly, fatigue levels improved initially but worsened slightly in the long term. These patterns suggest that while MSC therapy may exert short-term anti-inflammatory and analgesic effects, chronic mechanical and inflammatory processes may limit its long-term efficacy[30,31].

Functional performance tests—including the 30-second sit-to-stand and 6-minute walk tests—demonstrated clear improvements in the first two months, followed by a decline at two years. Interestingly, the Berg Balance Scale scores improved post-treatment and were largely

preserved over the long term, indicating that MSC therapy may have relatively lasting benefits on balance and general motor control. WOMAC scores also significantly improved in the early period; although a deterioration was noted at the 2-year follow-up, the scores remained significantly better than baseline, suggesting a partial sustained benefit in terms of pain and function[27,29].

Subjective patient feedback indicated that those who engaged in regular exercise experienced better clinical outcomes. In contrast, those who reported early recurrence of pain typically did not adhere to an exercise regimen. This emphasizes the importance of rehabilitation in optimizing treatment outcomes26. Patients who required knee arthroplasty or a second MSC injection represented the group that did not respond adequately to the initial therapy.

When compared with the existing literature, MSC therapy continues to emerge as a promising alternative to conventional non-surgical treatments for OA, such as nonsteroidal anti-inflammatory drugs, corticosteroids, and hyaluronic acid injections[26,27]. However, the efficacy of MSC therapy appears to vary based on patient age, MSC source (e.g., adipose tissue, bone marrow, synovium, umbilical cord), dosage, and follow-up duration14,28. Studies suggest that adipose-derived MSCs (AD-MSCs) may be more effective than bone marrow-derived MSCs (BM-MSCs), and that higher doses are beneficial in the short term, although they may also increase the risk of side effects[27,29]. Most current studies have limited follow-up durations (typically ≤12 months), and the in vivo longevity of MSCs remains a concern, making long-term evaluation challenging14,26. Consequently, future studies should adopt longer follow-up periods and optimized dosing protocols. From a safety perspective, MSC therapy is generally well-tolerated, with serious adverse events being rare. Minor side effects such as localized pain and swelling at the injection site are most commonly reported. The use of ultrasound guidance during injection may enhance procedural safety[14,31]. However, both clinical outcomes (e.g., VAS, WOMAC) and imaging markers plateaued or slightly regressed after year 3, suggesting that the therapeutic effects of a single injection may diminish over time. These findings underscore the potential value of "booster" injections at regular intervals (e.g., yearly), as supported by recent studies[14]. Notably, subjective reports indicated better long-term outcomes among patients who adhered to regular physical activity, highlighting the synergistic role of rehabilitation alongside MSC treatment. In contrast, patients who reported early recurrence of pain or required further interventions (e.g., arthroplasty or second injection) tended not to follow rehabilitation protocols, emphasizing the need for patient education and structured post-injection exercise regimens[26].

This study has several limitations. First, the absence of a placebo or standard treatment control group limits the ability to definitively determine the true efficacy of adipose-derived stem cell (ASC) treatment. Including a control group would provide a more robust basis for comparing intervention effectiveness and controlling for potential placebo effects. Second, the lack of randomized controlled trials in this field highlights the need for further research under controlled conditions, especially considering that key treatment parameters such as optimal stem cell dosage and dosing schedule remain unclear. Future research should begin with small-scale feasibility studies to refine treatment protocols, followed by larger pragmatic controlled trials that better reflect routine clinical practice. This approach would strengthen the evidence base and facilitate integration of ASC therapy into standard care for hip osteoarthritis. Finally, this study did not include post-treatment imaging assessments, which limits insight into structural changes such as cartilage repair, synovial inflammation, or bone remodeling within the hip joint. Understanding these structural changes is critical to determining whether the observed clinical improvements correspond to true disease modification. To address this limitation, future studies should incorporate baseline imaging and serial follow-up scans at defined intervals (e.g., 6 and 12 months).

Conclusion

This retrospective study demonstrates that MSC therapy in patients with knee OA provides significant short-term improvements in pain, function, and balance. However, partial deterioration in some clinical parameters was observed over a 2-year period. The high dropout rate and diminished functional gains over time necessitate cautious interpretation regarding the long-term efficacy of MSC therapy. Regular exercise and rehabilitation appear to play a critical role in sustaining treatment benefits.

While MSC therapy represents a promising non-surgical alternative for OA management, optimization of cell source, dosage, and administration protocols is essential. Future prospective, long-term randomized controlled trials are needed to more definitively establish the efficacy, safety, and optimal implementation strategies for MSC-based treatments in osteoarthritis.

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Table 1: A Follow-up Results on Knee Function in Osteoarthritis Patient

	[1]Pre-therapy Mean (SE)	[2]Post-therapy Mean (SE)	[3]Post-therapy Mean (SE)	[4]Two-years fallow-up	p value	Post-hoc 1, 2, 3 (p)
	Range of Motion[0]					
Dominant[0]	116 (3.1)	123 (1.8)	127 (1.3)	115.5 (3.0)	0.0001	1-2 (0.004) 1-3(0.000) 2-3 (0.017) 1-4 (0.06)
Non-Dominant[0]	120 (2.2)	125 (1.8)	128 (1.3)	115 (2.3)	0.001	1-2 (0.002) 1-3(0.000) 2-3 (0.102) 1.4 (0.04)
Pain VAS	8 (0.5)	6.4 (0.4)	5.1 (0.3)	7.3 (2.4)	0.001	1-2 (0.002) 1-3(0.000) 2-3 (0.014) 1-4 (0.227)
Fatigue VAS	7.4 (0.4)	5.8 (0.4)	4.7 (0.4)	6.11 (2.4)	0.001	1-2 (0.002) 1-3(0.000) 2-3 (0.001) 1-4 (0.01)
30 sec Stand Sit Test (sec)	6.8 (0.5)	8.4 (0.5)	10.08 (0.5)	7.47 (3.1)	0.001	1-2 (0.002) 1-3(0.000) 2-3 (0.002) 1-4 (0.09)
6 min Walking (m)	202 (20.5)	442 (20.9)		272.3 (20.6)	0.001	1-2 (0.001) 1-4 (0.03)
BERG Balance Total Score	37.8 (2.2)	43.9 (2.1)	46.3 (1.9)	43.1 (1.5)	0.001	1-2 (0.000) 1-3(0.000) 2-3 (0.033) 1-4 (0.005)
WOMAC Total Score	80.2 (4.5)	60.11 (4.4)	44.22 (4.2)	65.8 (5.1)	0.001	1-2 (0.003) 1-3(0.000) 2-3 (0.003) 1-4 (0.01)