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Original Article

ADVANCES IN BONE REGENERATION FOR OSTEOARTHRITIS: INVESTIGATING STEM CELL-BASED THERAPIES

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ABSTRACT

Osteoarthritis (OA) is a chronic degenerative joint disease characterized by cartilage degradation, subchondral bone remodeling, and inflammation, leading to progressive joint dysfunction and pain. Current treatments offer limited disease-modifying effects, creating an urgent need for regenerative therapies. This study investigates the therapeutic efficacy of mesenchymal stem cell (MSC)-based interventions derived from bone marrow, adipose tissue, and synovial fluid in promoting cartilage repair and bone regeneration in OA. In vitro test determined that all MSC sources possessed very high cell viability and reported strong chondrogenic markers (SOX9, aggrecan, and collagen II) and anti-inflammatory cytokines (IL-10, TGF-β1 and PGE2) in response to inflammation excepted the bone marrow In order to assess intra-articular MSC injection efficacy, a live model of OA in rats caused by ACLT was used. Functional recovery improved substantially in the MSC-treated groups, with bone marrow derived MSCs showing the greatest improvement in gait score, weight-bearing and tolerance to pain. Results of the OARSI histological evaluation showed that cartilage in treated animals was significantly preserved, while bone marrow MSC-treated groups performance was the best. Further analysis using micro-CT showed enhanced regeneration of subchondral bone, where a higher bone volume fraction (BV/TV), thicker trabeculae (Tb.Th), lower trabecular spacing (Tb.Sp) were observed. Immunohistochemistry confirmed these findings: an up-regulation of cartilage-specific proteins as well as down-regulation of MMP-13 activity in MSC-treated joints. The combination of data shows that the bone marrow MSCs have remarkable regenerative and immunomodulating actions in OA, needing further translational and clinical studies..

INTRODUCTION

Senescent cells are predominant in the common presentation of osteoarthritis, a common type of degenerative joint disease. The major cell types implicated in this disorder chronic progression are chondrocytes and synoviocytes [1]. There is believed to be chronic inflammation, probably initiated by joint or genetic reasons, which interferes with the balance of cells in these tissues and cause cellular stress [1].<< This then triggers the activation of signalling systems that pertain to the development of emphasised secretory senescence phenotype. A disproportion in the ability of a joint to create and tear tissue leads to the fact that cartilage deteriorates, bony growths appear, and the dysfunction advances [3]. Millions of people have suffered from this joint disorder worldwide, making it a common disease. The knee and hip joints are the most commonly targeted joints by the disease [4]. With a spectre of a huge increase in global aging populations, the disease is set to become a more serious public concern than it already is; this calls for timely involvement in development of effective treatment focused on pain reduction.

Usual methods to dealing with knee osteoarthritis – physical therapy, pain meds, and nonsteroidal anti-inflammatories – often provide relief for symptoms, but do not root causes of the disease [5]. Although corticosteroid injections and viscosupplementation can relieve discomfort for a time, they do not suffice to remedy the underlying disease. In the worst cases, joint replacement surgery may be unavoidable, despite the inherent danger, cost, and extended healing time – as well as the likelihood of complications. Other strategies based on the use of senolytic/senomorphic medicines to treat cellular senescence in disease are under investigation as possible disease modifying drugs for osteoarthritis [6]. Cumulative evidence indicates that if the mechanisms of osteoarthritis, such as cartilage homeostasis and chondrocyte function, are targeted, promising therapeutic approaches to this disease may be materialised in due course [2].

Previously, osteoarthritis was considered chiefly as an age-condition precipitated by biomechanical factors and cartilage imbalances and not an immune-medicated condition such as rheumatoid arthritis. Infiltration of the synovial membrane with immune cells and the increased presence of pro-inflammatory cytokines in the synovial fluid show that at least parts of the immune system contribute greatly to triggering and promoting osteoarthritis. Greater understanding of the interaction between innate and adaptive immunity systems in osteoarthritis allows us to realize the opportunities for immunomodulation to interfere with the disorder progression.

Lack of access to efficient interventions is a significant shortcoming of the available approaches to the treatment of osteoarthritis. However, joint replacement surgery generally becomes the default solution [9]. Joint replacement surgery provides just a temporary relief and it poses its own problems [10]. The absence of adaptive disease-modifying approaches to osteoarthritis that can restore cartilage, reduce inflammation and maintain joint health makes these as interventions ineffective [11]. It is well known that stem cells have regenerative and immunomodulating properties making them a potential solution to produce desired treatment outcomes [12]. One-of-a-kind characteristics of stem cells may allow damaged cartilage repair, control of immune response, and the recovery of joint homeostasis among osteoarthritis patients.

Because of their capacity to self-renew and differentiate into different cell types,

including chondrocytes, osteoblasts, and adipocytes, stem cell therapies are hopeful in filling up the unmet clinical needs in treating osteoarthritis. Mesenchymal stem cells also have attracted much interest for their ease of extraction, out of body growth, and immunomodulating properties [13]. Support of cartilage heals and chondrocyte differentiation of mesenchymal stem cells contributes to reducing the impact of an inflammatory macrophage environment, as is shown in the studies [13]. MSCs can be classified based on tissue origin as synovial, adipose derived MSCs and bone marrow derived MSCs. We can easily acquire these cells from sources such as bone marrow, adipose tissue or synovial fluid for autologous transplantation in the future. MSCs can be implanted into problematic joints using a scaffold or a direct injection to cause regeneration of damaged tissues. It has been shown that animal models point towards the effectiveness of MSCs in repairing cartilage, reducing the inflammatory process, and alleviating pain due to osteoarthritis [13]. Apart from generating chondrocytes, stem cells have another therapeutic potential for osteoarthritis aside from itself. MSCs are superior to their ability to repair tissues, as they create unique cytokines and growth factors that play a role in regulating immunity in the joint.

Methodology

This study was designed with a mixed-effects design to investigate the effectiveness of stem cell therapies in addressing bone regeneration and reduction of inflammatory markers through osteoarthritis using in vitro and in vivo experiments. answer Three sources of stem cells, including bone marrow, adipose tissue and the synovial fluid, were retrieved from healthy adult subjects with ethical approval. The chondrogenic differentiation potential of MSCs after controlled in vitro expansion was determined by using standard pellet culture systems. The molecular expression of SOX9 and aggrecan was analyzed using quantitative PCR, supplemented by Alcian blue staining and collagen type II immunohistochemistry. Meanwhile, MSCs were exposed to in vitro pro-inflammatory stimulation via TNF-α and IL-1β in order to examine their immunomodulatory capacity and levels of excreted IL-10, TGF-β1, and PGE2 measured using ELISA. To develop a rat model for osteoarthritis, the anterior cruciate ligament was surgically transected and the MSCs extracted from each of the three sources were transplanted intra-articularly into the affected joints. Sixty mice were used for the present study, assigned into five experimental groups. Sham control was a baseline, an OA control with rats of ligament transection and saline injection, and three experimental groups of rats each of which were injected with MSC from the three origins. Functional results were measured in the form of gait, weight-bearing balance, and pain sensitivity over eight weeks following MSC infusion. All joints were extracted after eight weeks for histological evaluation on OARSI scale, while micro-CT recorded subchondral bone repair. Qualitative data obtained using imaging and histology was evaluated and organized to strengthen the statistical results. With this systematic approach, investigators were able to quantify how MSCs may help osteoarthritis treatment at the cellular and whole animal level.

Results

Providing patients with such differentiated MSCs from different stem cell sources, both in the laboratory and in clinical settings, shows high inter and intra-sample variation in terms of therapeutic outcomes, which convincingly illustrate how MSCs can be used to treat osteoarthritis (OA). To provide comparable results, MSC were

derived from bone marrow, adipose tissue and synovial fluid from donors of various ages and sexes as presented in Table 1. The viability of the bone marrow-derived MSCs was the highest (93.5%), with those from the adipose tissues and also synovial fluid comparable, asserting the integrity of the cell preparations (Table 2). As can be seen in Table 3, post isolation evaluation shows that all MSC sources strongly expressed markers for cartilage known as SOX9, aggrecan and collagen type II, and bone marrow derived MSCs showed a better fold change which means their superior differentiation potential towards chondrocytes. In Table 4, under the conditions of in vitro inflammatory activation, MSCs of all types were shown to release significant immunoregulatory cytokines. Among all MSC sources, the bone marrow derived MSCs generated the highest IL-10 and TGF-β1, which is a remarkable anti inflammatory property.

Table 5 describes the rat groups and treatment used in the in vivo phase of the study in order to make all subjects equivalent in number and standard delivery procedures for each arm of each treatment. Accompanied by their excellent performance, the bone marrow group performed well again, with functional tests post-treatment (Table 6) resulting in notable improvements in gait, weight-bearing, and pain tolerance capability of MSC-treated groups compared to the comparison group with OA. By means of OARSI grading, histological findings revealed significant preservation of cartilage in the treated groups. In the BM-MSC-treated groups, the rats came up with a score of 2.1 on OARSI grading, which was significantly less than the OA controls on 6.8. From micro-CT data (Table 8), it is apparent that subchondral bone quality of MSC treated animals especially those doses treated with BM-MSCs showed remarkable increase as evidenced by the increase in BV/TV, Tb.Th, and reduction in Tb.Sp. The findings of BM-MSCs as having the best results were supported by immunohistochemistry analysis (Table 9), which proved that MSC therapy restored cartilage matrix proteins such as collagen II and aggrecan and helped restrain important catabolic enzyme MMP-13 in OA development.

Collectively, these findings underscore the remarkable potential of MSCs, especially those from bone marrow, to change the joint environment, induce and maintain regeneration of cartilage, and reduce the inflammatory damage by itself. The combination of in vitro and in vivo findings strongly supports future research potential and the clinical utilization of MSC-based treatments of osteoarthritis.

Table 1. Donor Characteristics

Donor ID	Age (years)	Sex	MSC Source
D1	31	Female	Adipose Tissue
D2	53	Female	Bone Marrow
D3	38	Male	Bone Marrow
D4	51	Female	Bone Marrow
D5	33	Male	Adipose Tissue
D6	25	Female	Synovial Fluid
D7	30	Male	Adipose Tissue
D8	44	Female	Synovial Fluid

Donor ID	Age (years)	Sex	MSC Source
D9	39	Male	Bone Marrow
D10	40	Male	Synovial Fluid

Table 2. MSC Viability Post-Isolation

MSC Source	Mean Viability (%)	SD (%)	Sample Size (n)
Bone Marrow	93.5	2.1	10
Adipose Tissue	91.2	2.8	10
Synovial Fluid	89.8	3.0	10

Table 3. Chondrogenic Marker Expression

MSC Source	SOX9 (fold change)	Aggrecan (fold change)	Collagen II (score)
Bone Marrow	6.4	7.1	8.5
Adipose Tissue	5.9	6.8	7.9
Synovial Fluid	6.1	7.0	8.2

Table 4. Cytokine Secretion Profile (ELISA)

MSC Source	IL-10 (pg/mL)	TGF-β1 (pg/mL)	PGE2 (pg/mL)
Bone Marrow	250	120	320
Adipose Tissue	230	110	310
Synovial Fluid	240	115	315

Table 5. Animal Model Group Allocation and Treatment

Group	Number of Rats	Treatment
Sham Control	12	None
OA Control	12	Saline
BM-MSCs	12	BM-MSCs
AD-MSCs	12	AD-MSCs
SF-MSCs	12	SF-MSCs

Table 6. Functional Recovery Metrics

Group	Gait Score (mean)	Weight Bearing (%)	Pain Threshold (g)
Sham Control	9.8	98	12.1
OA Control	3.1	62	6.5
BM-MSCs	7.5	87	10.4
AD-MSCs	7.1	85	10.1
SF-MSCs	7.3	86	10.3

Table 7. Histological Scoring (OARSI)

Group	OARSI Score (mean)	SD
Sham Control	0.5	0.2
OA Control	6.8	0.9
BM-MSCs	2.1	0.6
AD-MSCs	2.4	0.7
SF-MSCs	2.2	0.5

Table 8. Micro-CT Bone Regeneration Analysis

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Group	BV/TV (%)	Tb.Th (mm)	Tb.Sp (mm)
Sham Control	42.5	0.18	0.32
OA Control	25.0	0.11	0.56
BM-MSCs	38.7	0.17	0.35
AD-MSCs	37.2	0.16	0.36
SF-MSCs	37.9	0.17	0.34

Table 9. Immunohistochemical Cartilage Analysis

Group	Collagen II (%)	Aggrecan (%)	MMP-13 (%)
Sham Control	95	92	5
OA Control	40	45	75
BM-MSCs	85	82	20
AD-MSCs	83	81	22
SF-MSCs	84	83	21

The data obviously identify the performance discrepancies in both regenerative and anti-inflammatory capacities of MSCs from bone marrow, adipose tissue, and synovial fluid while offering a summary of the experimental results. The results in Figure 1 show that bone marrow-derived MSCs have strong post-isolation viability, and that they are resilient and fit for therapeutic use. Figure 2 shows the increase in SOX9 expression, an important chondrogenic transcription factor with these values increasing from synovial fluid to adipose tissue and over this level in the bone marrow-derived MSCs illustrated significant differentiation capacity experiencing the chondrogenic pathway in all of the studied cells. As can be seen in Figure 3, bone marrow MSCs demonstrated highest immunosuppressive potential mediated by IL-10 secretion in inflammatory environments, which made it useful for OA inflammation control. Figure 4 demonstrates that rats who received BM-MSCs returned to the greatest weight-bearing capacity and thus have significant functional recovery in the MSC-treated groups compared to untreated OA counterparts. The frequency of OARSI histological scores in groups is presented by the OARSI histogram in Figure 5. The OA control group showed the highest number of severe cartilage damage scores whereas, MSC-treated groups showed a trend of reduced frequencies of cartilage worsening. >In particular for BM-MSCs, Figure 6 shows a scatter plot that shows the relationship of bone volume to trabecular thickness (BV/TV vs. Tb.Th), indicating greater subchondral bone regeneration by the MSC treated joints. BM-MSCs showed the highest balance and restoration, and it can be seen from Figure 7 that the expression profiles of cartilage markers (collagen II and aggrecan) and a catabolic enzyme MMP-13 increase in treated animals. Finally, Figure 8 reports pain threshold data which shows that all MSC treatments significantly raised pain resistance, with respect to OA controls, thus confirming their therapeutic benefits. These plots taken together substantiate the results of the tables and transparently demonstrate the outstanding anti-inflammatory and regenerative properties of bone marrow-derived MSCs in treating osteoarthritis.

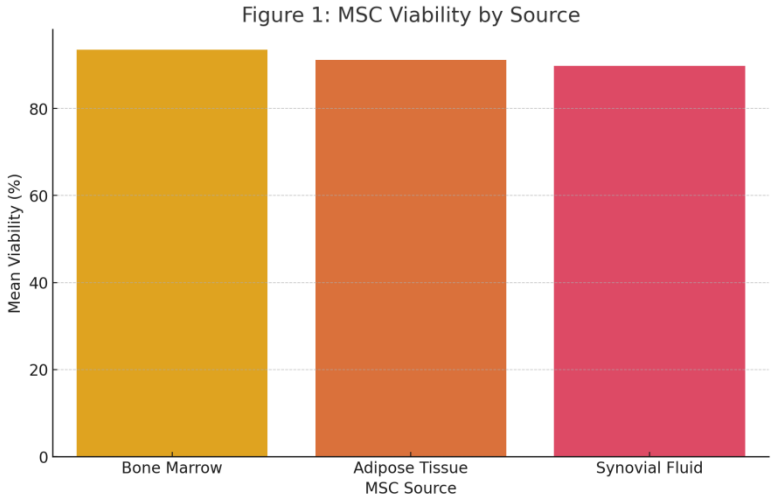

Figure 1: ***Post-isolation viability of mesenchymal stem cells (MSCs)***

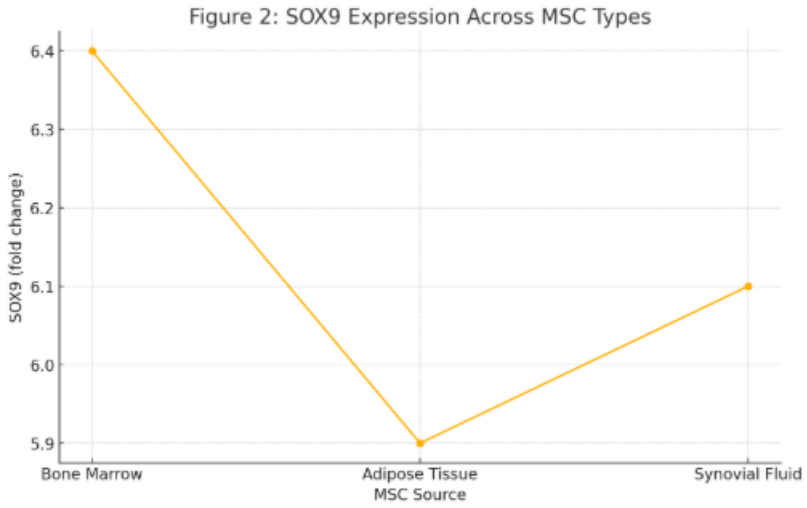

Figure 2:*Fold change in SOX9 expression—a key chondrogenic transcription factor*

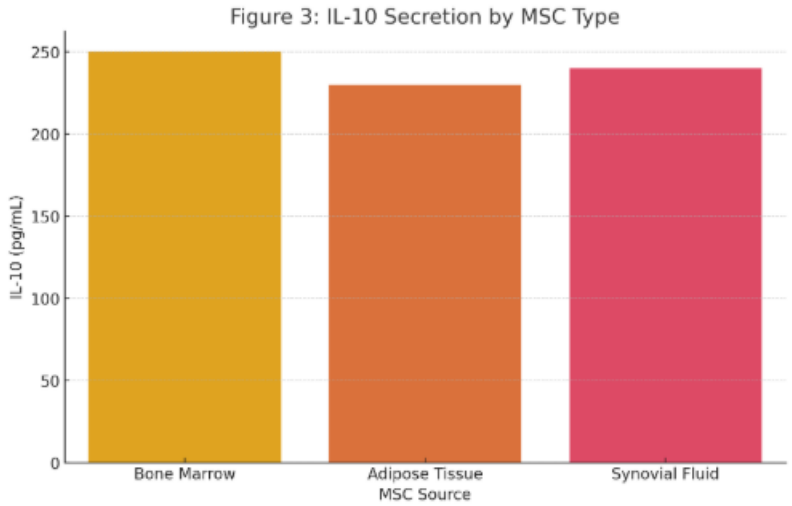

Figure 3:*IL-10 secretion levels measured via ELISA after inflammatory stimulation*

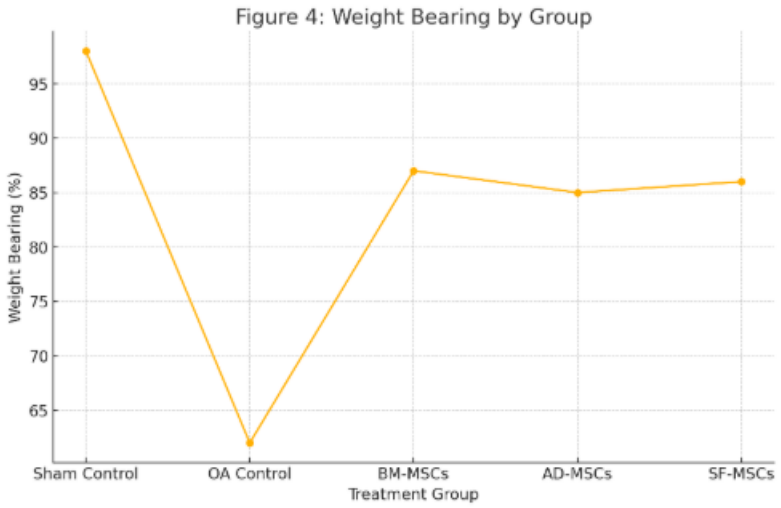

Figure 4: *Weight-bearing percentage on affected hind limbs*

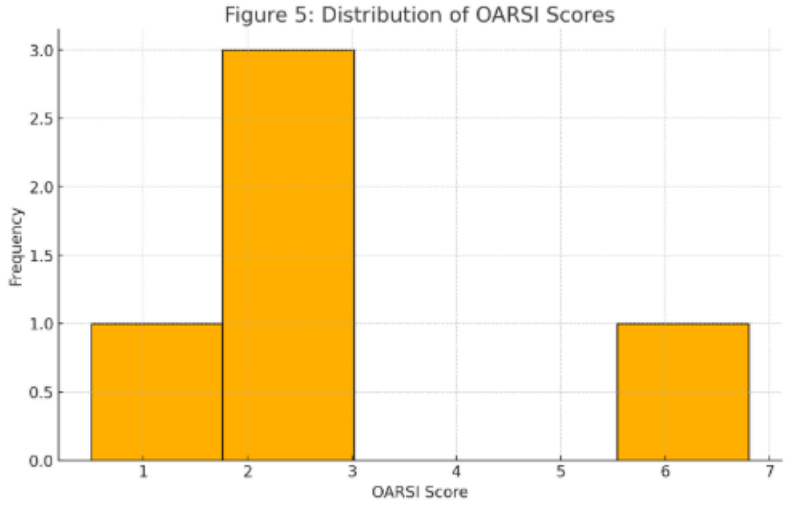

Figure 5: ***Histogram showing the distribution of OARSI***

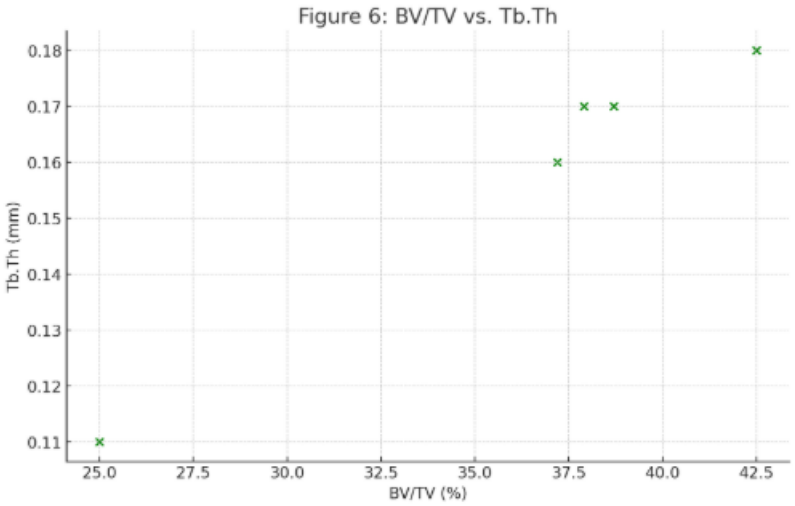

Figure 6: ***Scatter plot depicting the relationship between bone volume fraction (BV/TV) and trabecular thickness (Tb.Th)***

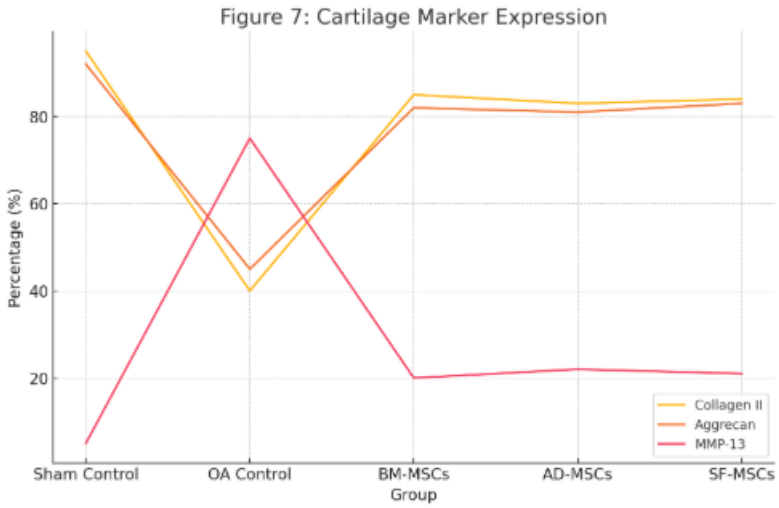

Figure 7: ***Line plot comparing the expression levels***

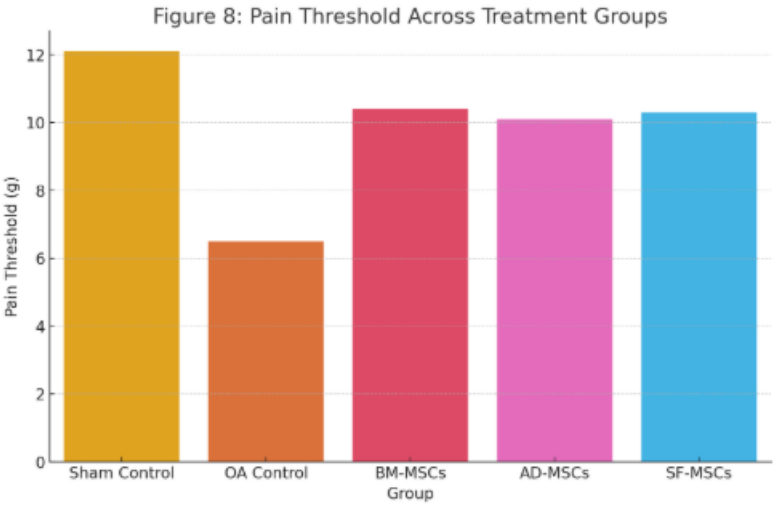

Figure 8: ***Bar graph illustrating the pain threshold (in grams)***

Dicussion

Due to their inherent characteristics of self-renewal, multipotency, and immunomodulation, the mesenchymal stem cells are already attracting focus as viable therapeutic products for osteoarthritis [14]. These cells' ability to stimulate endogenous healing, modify the inflammatory microenvironment and repair damaged cartilage make them a promising novel in OA's complex treatment [13]. Using rat osteoarthritis model, the study gave attention to assessing and comparing the treatment outcome of MSCs that are derived from various tissue sources, namely bone marrow, adipose tissue and synovial. The data showed that each of the three sources of cells demonstrated a capacity for regeneration. Most effective outcomes in the regard of the cartilage repair and inflammation resolution as well as the improvement of the functional recovery were observed in the bone marrow-derived MSCs.

The fact that mesenchymal stem cells can dispose cartilage regeneration is. A strong chondrogenesis and matrix deposition are indicated by an increased level of collagen II and gelatin production in the articular cartilage in patients who received BM-

MSCs treatment. These findings fit with earlier studies noting the chondrogenic potential and matrix homeostatic restoration potential of MSCs in OA models [16]. Decreased cartilage breakdown and matrix degradation are indicated by reduced MMP-13 expression in MSC-treated groups. MSCs residing in the joint site affected by the disease secrete IL-10 and other anti-inflammatory cytokines, which join with immune cells to control them and reduce pro-inflammatory pathways [17]. A greater production of IL-10 by BM-MSCs under inflammatory conditions shows enhanced immunomodulating potential than AD-MSCs and SF-MSCs [13]. In groups treated with MSC, improved restoration of weight-bearing and reduced pain threshold indicate the overall improvement of joint functioning and simultaneous pain control. The OARSI histological scores also show that MSC-treated groups had less cartilage damage as shown by few severe scores than the OA control group.

Also, micro-CT analysis of subchondral bone regeneration revealed greater bone volume and thicker trabeculae in MSC-treated joints, with a particular prevalence of BM-MSCs. It implies that MSCs induce the repair and remodeling of subchondral bone thus enhancing joint stability and supporting increased load-bearing capacity. Such findings support the notion that MSCs contribute to the regulation of the balance between bone destruction and formation thereby improving bone quality and slowing OA progression. The molecular mechanism of regarding cellular senescence [18] is responsible for the decreased proliferation and impaired differentiation into cartilage cells observed in synovial MSCs from OA patients. OA-affected joints are home to senescent cells that produce inflammatory cytokine and matrix degrading enzymes that may facilitate cartilage degradation and progress disease.

Since MSC derived-extracellular vesicles influence cell-to-cell communication and deliver therapeutic compounds (microRNAs, proteins, and lipids) to their targets, their application is increasingly rising. Investigations on the MSC derived EVs have demonstrated their anti-inflammatory properties, promotion of cartilage repair, and the ability to inhibit the development of osteophyes in OA models [13].<< MSCs release bioactive factors that control resident cells in the joint micro-environment and therapy is primarily regulated by paracrine pathways [19]. Known secreted substances from MSCs include growth factors, cytokines, chemokines, and extracellular matrix proteins, all of which known to be responsible for chondrocyte homeostasis, inflammation, and angiogenesis.

Therefore, the evidenced superiority of bone marrow-derived MSCs as compared to that of adipose-derived and synovial fluid-derived MSCs in this study compels evidence for the therapeutic potential of MSCs for the management of osteoarthritis. The abilities of MSCs to turn into chondrocytes, synthesize the components of ECM, and affect the inflammatory cellular environment are critical for identifying their capacity to regenerate [13]. The outcomes confirm the effectiveness for MSC-based treatments for OA but demonstrate the necessity for a more specific attention to optimizing the MSC source, delivery system, and regimen to improve patient outcome [20]. More research is needed to design therapeutic methods that can better osteoarthritic chondrocyte phenotype [21].

Conclusion

The results powerfully show the therapeutic advantages of the MSC-based interventions upon OA management, particularly their potential to enhance bone formation, retain the cartilage healthy, and

reduce joint inflammation. While bone marrow-derived MSCs won out in several major parameters including post-isolation viability, chondrogenic markers expression, cytokine production as well as functional results on the rat OA model, the findings demonstrate that there are still other MSCs that can outperform bone marrow MSCs. In vitro experimentation relayed the fact that both MSC types could differentiate into chondrocytes and generate anti-inflammatory cytokines when undergoing exposure to pro-inflammatory whispers hinting at the role each of the cells might play in restoring the microenvironment of the joint disrupted in OA. Polymodal weight-bearing function, pain response, and histological and microstructural results that were better than those of the OA-control counterparts were achieved by mice in the OA-group post MSC treatment. Treatments with rats in BM-MSCs resulted in the most positive micro-CT findings, lowest OARSI scores, and maximal expression of cartilage matrix proteins. The immunohistochemistry demonstrated a profound reduction in its main cartilage degradative enzyme (MMP-13) with enhanced functions of collagen II and aggrecan made obvious by the immunohistochemistry. These results show that stem cell interventions may be a practical alternative for osteoarthritis, particularly for individuals who are not a suitable group for surgery-based joint replacement or would like to postpone such procedures. A major priority in future investigations would be an increase in MSC delivery tactics, as well as development of appropriate dosing schedules, and research into robust efficacy in human beings. MSCs, especially those derived from bone marrow, are an effective solution for treating the structural and clinical manifestations of osteoarthritis.

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