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Review

Osteoarthritis and stem cell therapy in humans: a systematic review

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SUMMARY

Objective: Osteoarthritis (OA) is a leading cause of disability in the world. Mesenchymal stem cells (MSCs) have been studied to treat OA. This review was performed to systematically assess the quality of literature and compare the procedural specifics surrounding MSC therapy for osteoarthritis.
Design: PubMed, CINAHL, EMBASE and Cochrane Central Register of Controlled Trials were searched for studies using MSCs for OA treatment (final search December 2017). Outcomes of interest included study evidence level, patient demographics, MSC protocol, treatment results and adverse events. Level I and II evidence articles were further analyzed.
Results: Sixty-one of 3,172 articles were identified. These studies treated 2,390 patients with osteoarthritis. Most used adipose-derived stem cells (ADSCs) ($n = 29$) or bone marrow-derived stem cells (BMSCs) ($n = 30$) though the preparation varied within group. 57% of the sixty-one studies were level IV evidence, leaving five level I and nine level II studies containing 288 patients to be further analyzed. Eight studies used BMSCs, five ADSCs and one peripheral blood stem cells (PBSCs). The risk of bias in these studies showed five level I studies at low risk with seven level II at moderate and two at high risk.
Conclusion: While studies support the notion that MSC therapy has a positive effect on OA patients, there is limited high quality evidence and long-term follow-up. The present study summarizes the specifics of high level evidence studies and identifies a lack of consistency, including a diversity of MSC preparations, and thus a lack of reproducibility amongst these articles' methods.

Introduction

Osteoarthritis (OA) is the most common joint disorder in the world and the most common arthritis in the United States[1,2]. While worldwide prevalences of knee and hip OA are 3.8% and 0.85% respectively, this burden is likely underestimated.[3]

OA is the common end-point of many different pathologies. As such, its etiology is varied, involving both intrinsic joint and extrinsic environmental factors. Age, gender, menopause, genetics, nutrition and bone density often lead to increased susceptibility to OA. These systemic factors, in addition to mechanical factors such as weight/body mass index, injury, surgery, and deformity help determine the location and severity of an individual's OA[1]. Additionally, elevated inflammatory cytokines such as IL-1β and TNFα have recently been implicated in OA's pathogenesis.[4]

Existing treatments for OA are largely unsatisfactory. Pharmacologic management includes acetaminophen, aspirin and oral non-steroidal anti-inflammatory drugs (NSAIDs)[7,8]. Other options include capsaicin, duloxetine, topical NSAIDs and intra-articular corticosteroid injections[5–7]. These drugs are recommended secondarily to patient education, strengthening exercises, and weight loss. Physical and occupational therapy have also demonstrated beneficial effects[7,8].

These conservative treatments may be sufficient for early management, but their role in modifying underlying structural abnormalities is limited. The OA Research Society International suggests patients consider surgical interventions if daily pain persists for months and conservative management has failed[8]. Total joint replacements have thus become important in the management of severe OA. In elderly populations, the prevalence of joint replacements due to OA is 13.6%[9]. However, ongoing research aims to develop less invasive procedures for management.

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Less invasive procedures such as intra-articular injections of hyaluronic acid (HA), platelet rich plasma (PRP), hypertonic dextrose prolotherapy and anabolic cartilaginous agents are being studied as potential therapies[10–12]. Intra-articular injection of mesenchymal stem cells (MSCs) is an increasingly common adjuvant therapy that has shown promising results. A 2014 proof-of-concept trial demonstrated that intra-articular injection of MSCs into OA knees improved function and pain without adverse events[13]. Regeneration of hyaline-like articular cartilage was noted[13]. Critics, however, are skeptical of the quality of evidence and cost of cell-based therapies[14].

To date, few MSC-related adverse events have been noted[13]. In a systematic review of the safety of intra-articular therapy, 844 procedures (mean follow-up 21 months) were analyzed to find only four serious adverse events: one infection post-bone marrow aspiration that resolved with antibiotics, one pulmonary embolus two weeks after aspiration, and two adverse events reported as unrelated to the therapy. Other sequelae included pain, swelling and dehydration after aspiration[15]. A more recent assessment of adverse events of autologous stem cell therapies found they primarily included post-procedural pain or pain due to progressive degenerative joint disease in under 4% of the population.[16]

The International Society for Cellular Therapy developed criteria to define MSCs as plastic-adherent in culture conditions expressing CD105, CD73, and CD90, lacking expression of CD45, CD34, CD14 or CD11b, CD79alpha or CD19, and HLA-DR surface molecules, and possessing tri-lineage differentiation into osteoblasts, adipocytes and chondroblasts[17,18]. However, the term MSC is not always used in the literature with this definition in mind. Evidence supporting the immunomodulatory role of MSCs suggests the term “stem cell” is a misnomer and the name be changed to medicinal signaling cells[19], though this change has yet to be reflected in the literature. The immunomodulatory properties of MSCs, however, have been postulated to have the capacity to play a role in manipulation of the disease process. These properties include anti-inflammatory, anti-apoptotive, anti-fibrotic, angiogenic, mitogenic and wound-healing paracrine activity.[20,21]

MSCs can be harvested from several sites including bone marrow (BMSCs), adipose tissue (ADSCs), synovium (SDSCs) or peripheral blood (PBSCs)[18]. BMSCs and ADSCs have received considerable attention due to their ease of extraction[22]. Once removed, typically from the iliac crest, BMSCs can be expanded in culture and induced to various stages of differentiation[22,23]. Adipose tissue is abundant, making ADSC procurement easy and minimally invasive[24]. ADSCs can differentiate into fat, bone or cartilage[25]. These cells are harvested from infra-patellar fat pads or subcutaneous sites such as the buttocks[26]. There is debate regarding the differences between BMSCs and ADSCs in terms of cell yield, growth kinetics, and differentiation capacity[24,27]. However, both animal and human models have shown positive results for OA treatment with these MSC types[28–30]. SDSCs, often harvested from the knee, are recognized for their differentiation potential and high cell yield[31]. PBSCs are collected via minimally invasive apheresis but are used less frequently[32]. When freshly collected, PBSCs do not display MSC markers unless in hypoxic conditions[33] or after subcutaneous administration of human granulocyte colony stimulating factor prior to blood draw[34].

The above MSCs can be isolated, culture-expanded and subsequently injected into joints. Other intra-articular formulations with one-step harvest and injection procedures are becoming popular, including injection of bone marrow aspirate concentrate (BMAC) containing BMSCs, stromal vascular fraction (SVF) isolated from lipoaspirate containing ADSCs, and microfragmented adipose tissue, a non-enzymatic approach to isolating the stromal vascular niche with ADSCs. SVF is isolated via liposuction, followed by collagenase digestion, centrifugation, and dilution[25,35,36]. BMAC contains a mixture of platelets, red and white blood cells, and hematopoietic and non-hematopoietic precursors. The term refers to the mixture of marrow elements and MSCs, but, after processing, only 0.001–0.01% of the cells are MSCs[37]. The SVF product contains MSCs, pericytes, fibroblasts, monocytes and macrophages, with 500,000 to 2,00,000 cells per gram of which 1–10% are considered ADSCs[35,36]. Microfragmented adipose tissue is obtained by harvesting lipoaspirate and washing off residues while adipose cluster dimensions are gradually reduced. Initial analysis has shown it contains preserved stromal vascular architecture with pericytes and MSCs[38].

Although MSC therapy has been used to treat articular cartilage repair for years, few clinical studies provide satisfactory levels of evidence to address the quality of available information. The Journal of Bone and Joint Surgery's (JBJS) Levels of Evidence rating scale defines parameters to help authors make level of evidence evaluations (level I, randomized controlled trial; level II, prospective cohort study or observational study with dramatic effect; level III, retrospective cohort study or case–control study; level IV, case series; level V, mechanism-based reasoning)[39]. These parameters help inform physicians' clinical decisions.

To our knowledge, there has been no systematic review which analyzes the effect of study quality and procedural specifics of both autologous and allogeneic MSC therapy for the treatment of OA. The aims of this investigation are to provide an analysis of the literature regarding the use of MSC therapy for OA treatment, to assess the quality of evidence, and to propose next steps for further investigation.

Methods

Search strategy

This review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines[40]. A literature search identified all articles involving stem cell therapy to treat osteoarthritis. PubMed, CINAHL, EMBASE and Cochrane Central Register of Controlled Trials were searched using “osteoarthritis” and “stem cell” MeSH terms presented in further detail in the appendix. Computer de-duplication was performed. The search was finalized in December 2017. Manual review of the references of selected articles was also completed to add studies that were originally missed.

Study selection

Two reviewers (DJ and AA) independently evaluated studies. Third and fourth reviewers (TE and EC) resolved any discrepancies for inclusion. After identifying the relevant studies through abstract information, studies were included after full-text evaluation. Inclusion criteria was any clinical study that used stem cells to treat osteoarthritis in humans. Outcome measures varied amongst articles. These measures included safety analyzed by the nature of adverse events, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), the Visual Analogue Scale (VAS) for pain, radiographic MRI or X-ray scores, as well as several others. Articles from any country were acceptable but limited to those published in the English language. Exclusion criteria were articles that did not use MSCs to directly treat OA patients, that were reviews, conference submissions/abstracts only or letters to the editor, that studied stem cells *in vitro*, that studied isolated, focal chondral defects not associated with OA, and that presented their research in a language other than English.

Data extraction and assessment of study quality

Authors (DJ and AA) independently extracted data using a template data extraction sheet, with third and fourth researchers (TE and EC) serving as tiebreakers if consensus was not achieved. Information gathered included study characteristics, patient demographics and outcomes. Primary outcome was the improvement, or lack thereof, in the patients' OA. Studies were rated on methodological quality according to The JBJS Levels of Evidence rating scale[39]. Risk of bias assessment was completed to evaluate each study's internal validity using Cochrane's Risk of Bias scale for randomized trials (RoB2.0)[41] and Risk of Bias In Non-randomised Studies – of Intervention (ROBINS-I) tool[42].

Analysis

Because of overall study heterogeneity and lack of adequate control groups, a formal statistical meta-analysis was attempted but not performed; however, pooled rates of several collected measures were calculated with the available data using Microsoft Excel when applicable.

Results

Literature search

The initial search of the three databases yielded a total of 3,416 articles. Nine articles were identified through other sources. Duplicates were removed and 3,172 articles remained. Of these articles, 381 were selected as relevant to the application of stem cell therapy for OA treatment. Of those articles, 61 were chosen to be discussed in this review due to their clinical nature. The PRISMA flow diagram can be visualized in Fig. 1. According to Marx, Wilson and Swiontkowski (2015), five studies classified as level I evidence, nine as level II, seven as level III, thirty-five as level IV, and five as level V.

Levels I–V (all clinical studies): study characteristics and intervention details

In total, the 61 studies enrolled 2,390 OA patients to be treated with MSC therapy. Table I gives an overview of study characteristics, while Table II[13,29,30,43–100] provides individual study details organized by level of evidence. Of the total study population, 2,662 joints were treated and 46% were female ($N = 1095$). OA sites included knee (51 studies), hand (2 studies), ankle (3 studies), shoulder (1 study), hip (2 studies) or multiple joints (2 studies with knee, hip and ankle).

In the 61 clinical studies, MSC type varied between ADSCs (29 studies), BMSCs (30 studies), and PBSCs (3 studies), and allogeneic umbilical cord-derived MSCs (1 study), taking into account that two studies used both ADSCs and BMSCs[62,86]. Among these studies, the processing and injected/implanted form also differed. ADSCs were either culture-expanded ($n = 3$), within SVF ($n = 24$) or micro-fragmented adipose tissue ($n = 2$). BMSCs were either culture-expanded ($n = 18$), within BMAC ($n = 10$), or allogenic ($n = 2$). Three studies used PBSCs and one study used allogeneic umbilical cord-derived MSCs. Several adjuvants were injected/implanted with the MSCs, including PRP ($n = 20$), platelet lysate ($n = 8$), and hyaluronic acid ($n = 10$). The median follow-up time was 12 months with a range of 3–84 months.

To better understand the quality of the literature pertaining to MSCs as OA therapy, the fourteen Level I and Level II articles were analyzed further.

Levels I–II only: study characteristics

Of the fourteen Level I and Level II evidence articles, 288 total patients were studied. Sixty-three percent of these patients were female ($n = 181$). Thirteen studies treated knee OA and 1 treated hand OA. Study characteristics of the Level I and II studies can be found in Table II. As depicted in Table III, the RoB 2.0 and ROBINS-I risk of bias quality assessment yielded five studies at low risk of bias, seven at moderate/some concerns risk, and two at high risk.

Levels I–II only: intervention details

In the Levels I and II cohort, 288 patients received MSC therapy. MSC regimen varied; a summary of the intervention details can be found in Table IV. Eight studies used BMSCs collected from the iliac crest. Of these, four were culture-expanded, 2 were BMAC and 2 were allogeneic. Five studies used ADSCs with four derived from abdominal fat and one from the buttocks. Of these five studies, 3 were culture-expanded injecting a range of 2×10^6 to 100×10^6 ADSCs and 2 were from SVF injecting a magnitude of 10^7 SVF cells with one study estimating this as 4.11×10^6 ADSCs[85]. Turajane, Chaveewanakown, Fongsarun, Aojanepong and Papadopoulos (2017) was the only one of these studies to inject 3 ml PBSCs containing a range of $1.095–1.276 \times 10^6$ total nucleated cells. This study employed three injections and compared groups that received microdriling, PBSC, growth factor addition, and HA (group 1) vs PBSC, PRP, HA (group 2) vs HA alone (group 3). The mean follow-up length of time for all studies was 14 ± 7 mo (Range 6 to 24)[93].

Outcome assessments

All 61 clinical studies reported some level of improvement of OA symptoms from baseline in the MSC therapy group. Main findings of outcome assessments in level I and II studies can be found in Table V[13,29,30,87]. Although there was overlap between outcome measures between included Level I and II articles, no meta-analysis was performed due to the diversity of metrics and outcomes. The most common measures were VAS ($n = 10$), WOMAC ($n = 9$), safety ($n = 6$) and radiologic evidence ($n = 5$).

Of the ten level I and II evidence studies that measured VAS for pain, patients in all of the studies exhibited VAS score improvements[29,30,87–92,94,97]. In four of these studies, VAS improved compared to placebo[29,30,87,91,94]. Lamo-Espinosa *et al.*[87] found the high-dose BMSC-treated patients' VAS improved significantly ($P < 0.01$) compared to placebo of HA alone. Garay-Mendoza *et al.*[29] found VAS improvements at 1 week ($P = 0.0003$), 1 month ($P < 0.0001$), and 6 months ($P < 0.0001$). Notably, the BMSC-treated group VAS pain score (0.92 ± 1.29) was lower compared to the daily acetaminophen placebo group (4.64 ± 2.43). Vega *et al.*[94] found BMSC-treated patients demonstrated significant VAS improvement at 6 months, whereas placebo HA-treated patients did not significantly improve until 12 months. Similarly, Koh *et al.*[91] found that both ADSC-treated patients and PRP-placebo patients improved their VAS scores at 6 and 12 months, but the ADSC-treated group demonstrated a greater VAS improvement (10.2 ± 5.7) than the placebo group (16.2 ± 4.6). Additionally, Nguyen *et al.*[30] found the ADSC-treated group (3.47 ± 0.74) improved significantly compared to the microfracture placebo group (2.08 ± 1.08). The remaining studies measuring VAS exhibited improvement upon follow-up but the improvement was either not statistically significant[89], not compared to the placebo[88], or there was no placebo to compare to[90,97]. One study showed VAS improvement with MSC treatment but no significance when compared to saline injection placebo ($P > 0.09$)[92].

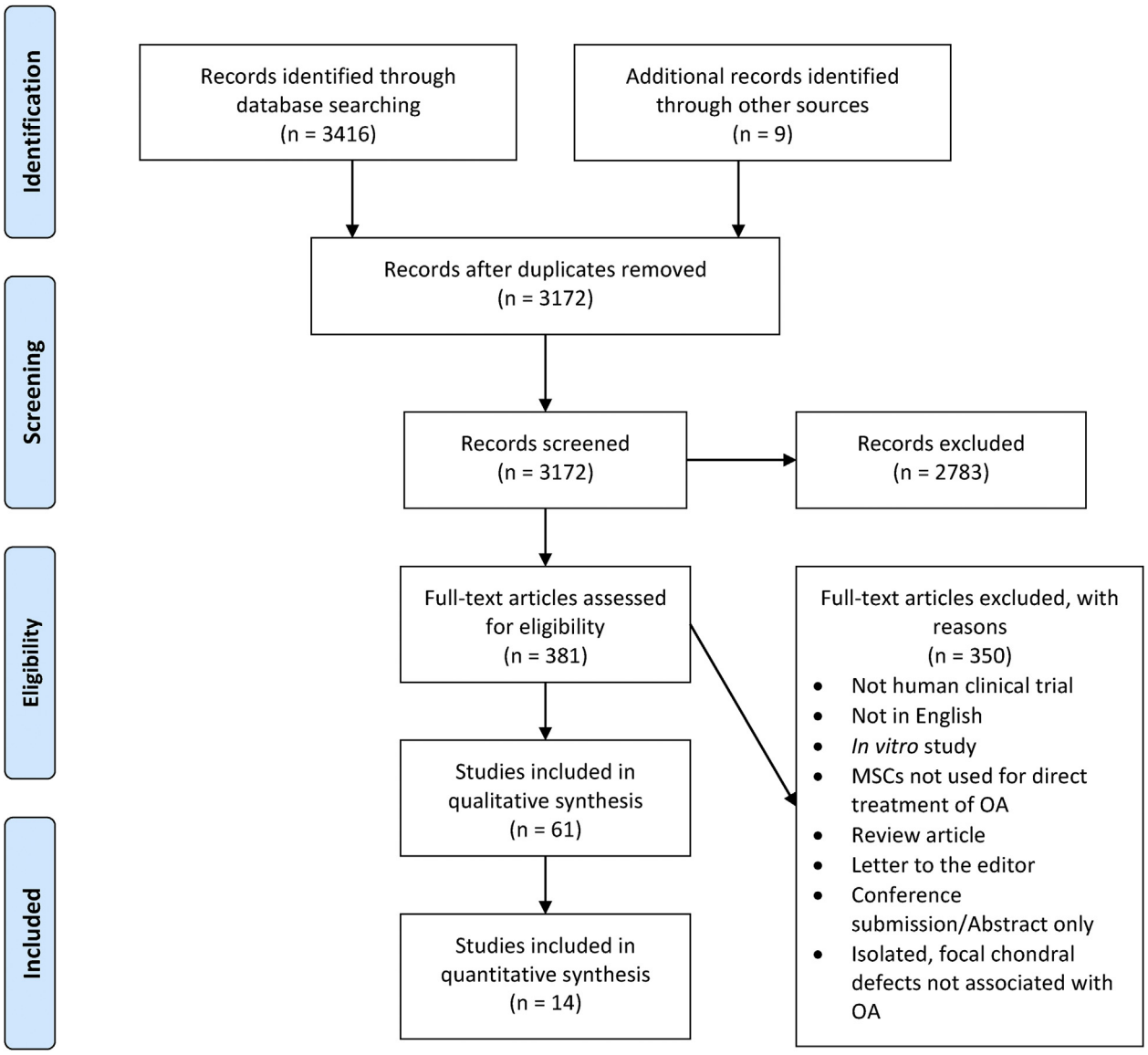

Fig. 1. Osteoarthritis and stem cell therapy PRISMA flow diagram.

Table I
Overview of the included clinical studies

N* (male/female)	OA site		MSC type†			Levels of evidence‡	
2,390 (1095/1315)§	Knee	51	ADSC 29	CE	3	I	5
	Ankle	3		SVF	24	II	9
				Micro	2		
	Hand	2	BMSC 30	CE	18	III	7
	Shoulder	1		BMAC	10	IV	35
	Hip	2		Allog			2
	Multiple Knee/Hip/Ankle	2	PBSC	3		V	5
			Allog hUCB-MSCs	1			

ADSC = adipose-derived stem cell; BMSC = bone-marrow stem cell; MSC = mesenchymal stem cell; OA = osteoarthritis; PBSC = peripheral blood stem cell.
CE: culture-expanded; Allog: allogeneic; Micro: microfragmented; hUCB-MSCs: human umbilical cord blood-derived mesenchymal stem cells.
* Number of patients treated with stem cell therapy.
† 2 studies used both SVF/ADSC and BMAC/BMSC[26,57].
‡ Levels of evidence according to Marx, Wilson, & Swiontkowski (2015)[56].
§ Based on total number of joints of those studies that reported gender (6 studies did not report gender by joint)[72,81,85,95,82].

Table II
Study characteristics of the included clinical studies grouped by level of evidence

First Author (Date of publication)	Country of origin	Level of evidence[56]	N* (Male/Female)	OA site	MSC Source/Type	Biologic adjuvant	Outcome measures	Follow-up length of time
Garay-Mendoza (2017)[29]	Mexico	I	30 (7/23)	Knee	BMAC/BMSC	Outpatient SQ G-CSF x 3 days	VAS WOMAC	6 mo
Gupta (2016)[89]	India	I	40 (12/28)	Knee	Allogeneic culture-expanded BMSC	PLASMALYTE-A Pre: Hydrocortisone and pheniramine maleate Post: Hyaluronic acid	VAS for pain ICOAP WOMAC WORMS – knee	12 mo
Lamo-Espinosa (2016)[87]	Spain	I	20 (12/8)	Knee	Culture-expanded BMSC	Hyaluronic acid	VAS WOMAC RoM X-Ray knee joint space width WORMS	12 mo
Turajane (2017)[93]	Thailand	I	40 (13/27)	Knee	PBSC	Hyaluronic acid, GFA (PRP, hG-CSF)	Need for surgical intervention at 12mo WOMAC	12 mo
Vega (2015)[94]	Spain	I	15 (6/9)	Knee	Allogeneic culture-expanded BMSC	n/a	VAS WOMAC Lequesne functional index SF-12 life quality questionnaire MRI T2 mapping, PCI	12 mo
Centeno (2014)[88]	Denmark, Sweden, USA	II	6 (4/2)	Hand	Culture-expanded BMSC	Platelet lysate	Percent pain relief Modified VAS Strength, ROM	12 mo
Jo (2014)[13]	Korea	II	18 (3/15)	Knee	Culture-expanded ADSC	n/a	WOMAC Safety Secondary: VAS, KSS, radiographic, histologic evaluation	6 mo
Jo (2017)[90]	Korea	II	18 (3/15)	Knee	Culture-expanded ADSC	n/a	WOMAC KSS KOOS VAS for pain MRI evaluation including cartilage defect size	24 mo Follow-up Jo (2014)[14]
Koh (2014)[91]	Korea	II	21 (5/16)	Knee	SVF/ADSC	PRP	KOOS Lysholm score X-Ray (femorotibial angle, weight-bearing line) Second-look arthroscopy evaluation of cartilage – Kanamiya grading system	Mean 24.2 ± 4.7 mo
Nguyen (2016)[30]	Vietnam	II	15 (3/12)	Knee	SVF/ADSC	PRP	WOMAC Lysolm score VAS for pain Modified Outerbridge classification	18 mo
Pers (2016)[97]	France, Germany	II	18 (8/10)	Knee	Culture-expanded ADSC	n/a	VAS for pain WOMAC Patient Global Assessment KOOS SAS SF-36 OARSI/OMERACT Responders	6 mo
Shapiro (2017)[92]	USA	II	25 (7/18)	Knee	BMAC/BMSC	Platelet-poor bone marrow plasma	VAS for pain ICOAP WOMAC KOOS Activity level	6 mo

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Table II (*continued*)

First Author (Date of publication)	Country of origin	Level of evidence[56]	N* (Male/Female)	OA site	MSC Source/Type	Biologic adjuvant	Outcome measures	Follow-up length of time
Wakitani (2002)[95]	Japan	II	12 (X/X)	Knee	Culture-expanded BMSC	Collagen gel sheet	Hospital for Special Surgery Knee Rating Scale Arthroscopic and Histologic cartilage evaluation	Mean: 16 months
Wong (2013)[96]	Singapore	II	28 (15/13)	Knee	Culture-expanded BMSC	Hyaluronic acid	Tegner activity score Lysholm score IKDC ICRS MOCART	2 yrs
Centeno (2015)[46]	USA	III	373 (283/126)	Knee	BMAC/BMSC	PRP, Platelet lysate	NPS LEFS Subjective Improvement Rating Scale IKDC	Varied by outcome, at least 12 mo
Centeno (2014)[44]	USA	III	681 (516/324)†	Knee	BMAC/BMSC ± SVF/ADSC	PRP, Platelet lysate	NPS LEFS Subjective Improvement Rating Scale	12 mo
Kim (2015)[60]	Korea	III	56 (22/32)†	Knee	SVF/ADSC	Group 1: n/a Group 2: fibrin glue product	IKDC Tegner activity scale ICRS grade	Mean 28.6 ± 3.9 mo (Range 24–34 mo)
Kim (2016)[61]	Korea	III	26 (11/15)	Ankle	SVF/ADSC	n/a	VAS for pain AOFAS Radiological talar tilt angle ICRS grade	Mean 27.7 ± 2.4 mo (Range 24–34 mo)
Kim (2015)[62]	Korea	III	40 (14/26)	Knee	SVF/ADSC	Injection group: PRP Implantation group: Fibrin glue product	IKDC Tegner activity scale ICRS grade	Injection group: 28.5 ± 4.8 mo Implantation group: 28.8 ± 4.0 mo
Kim (2016)[63]	Korea	III	31 (15/16)	Ankle	SVF/ADSC	n/a	VAS for pain AOFAS Radiological tibial ankle surface, tibial lateral surface and talar tilt angle ICRS grade	Mean 27.6 ± 5.0 mo
Koh (2012)[91]	Korea	III	25 (8/17)	Knee	SVF/ADSC	PRP	Lysholm score Tegner activity scale VAS for pain	Mean 16.4 ± 2.3 mo (Range 12–18 mo)
Ahmad (2014)[43]	Egypt	IV	10 (3/7)	Knee	PBSC	n/a	WOMAC 6MWD MOAKS	12 mo
Bansal (2017)[44]	India	IV	10 (6/4)	Knee	SVF/ADSC	PRP	WOMAC 6MWD X-Ray joint space width MRI articular cartilage thickness	2 yrs
Buda (2016)[45]	Italy	IV	56 (37/19)	Ankle	BMAC/ BMSC	Autologous platelet-rich fibrin	AOFAS MOCART	36 mo
Centeno (2011)[52]	USA	IV	135 (93/42)	Knee	Culture-expanded BMSC	Platelet lysate or PRP	Likert scale for reported pain relief	Mean 11.3 mo
Centeno (2015)[47]	USA	IV	34 (27/7)	Shoulder	BMAC/BMSC	PRP, Platelet lysate	DASH NPS Subjective Improvement Rating Scale	At least 3 mo
Davatchi (2011)[53]	Iran	IV	4 (2/2)	Knee	Culture-expanded BMSC	Physiological serum	VAS for pain Walking time to pain Number of stairs to pain Time to gelling pain RoM Patellar crepitus Swelling, Instability	6 mo
Davatchi (2016)[54]	Iran	IV	4 (2/2)	Knee	Culture-expanded BMSC	Physiological serum	Same as Davatchi (2011)[7] Patient Global Assessment	5 yrs Follow-up Davatchi (2011)[7]

Table II (*continued*)

First Author (Date of publication)	Country of origin	Level of evidence[56]	N* (Male/Female)	OA site	MSC Source/Type	Biologic adjuvant	Outcome measures	Follow-up length of time
Emadedin (2012)[23]	Iran	IV	6 (0/6)	Knee	Culture-expanded BMSC	n/a	VAS WOMAC Walking distance Time to gelling Patellar crepitus RoM MRI cartilage assessment	12 mo
Emadedin (2015)[55]	Iran	IV	17(X/X)	Ankle ($n = 6$) Hip ($n = 5$) Knee ($n = 6$)	Culture-expanded BMSC	n/a	VAS WOMAC HHS FAOS Walking distance Lab studies MRI analysis	30 mo
Fodor (2016)[56]	USA	IV	6 (1/7)†	Knee	SVF/ADSC	n/a	VAS for pain WOMAC RoM Timed up-and-go MRI - observational	1 yr
Gibbs (2015)[57]	Australia	IV	4 (2/2)	Knee	SVF/ADSC	PRP, Moderate exercise program	KOOS Physical function tests: GUG, SCT RPE	12 mo
Hudetz (2017)[58]	Croatia	IV	17 (12/5)	Knee	Microfragmented/ ADSC	n/a	VAS for pain dGEMRIC IgG Glycans	12 mo
Kim (2015)[26]	Korea	IV	49 (26/29)†	Knee	SVF/ADSC	Fibrin glue product	IKDC score Tegner activity scale Overall surgery satisfaction	Mean 26.7 ± 3.6 mo (Range 24–36 mo)
Kim (2016)[59]	Korea	IV	20 (9/15)†	Knee	SVF/ADSC	Fibrin glue product	IKDC Tegner activity scale MOAKS MOCART	Mean 27.9 ± 3.2 mo (Range 24–34 mo)
Koh (2015)[64]	Korea	IV	30 (5/25)	Knee	SVF/ADSC	PRP	KOOS Lysholm score VAS Second-look arthroscopy evaluation of cartilage	24 mo
Koh (2013)[65]	Korea	IV	18 (6/12)	Knee	SVF/ADSC	PRP	WOMAC Lysholm score VAS for pain WORMS	Mean 24.3 ± 0.8 mo (Range 24–26 mo)
Koh (2014)[67]	Korea	IV	56 (22/34)	Knee	SVF/ADSC	n/a	IKDC Tegner activity scale Patient satisfaction Second-look arthroscopy – ICRS	Mean 26.7 ± 2.5 mo
Mardones (2017)[68]	Chile	IV	10 (7/6)†	Hip	Culture-expanded BMSC	n/a	VAS WOMAC HHS VAIL hip score Tönnis Classification of Osteoarthritis	Range 16–40 mo
Murphy (2017)[70]	Ireland	IV	13 (2/11)	Thumb – CMC joint	BMAC/BMSC	Tisseel	VAS RoM Kapandji opposition score Strength (pinch test) DASH Grind test	12 mo
Oliver (2014)[86]	USA	IV	70 (21/49), 122 knees	Knee	BMAC/BMSC + SVF/ADSC	n/a	KOOS Adverse events	180 days
Orozco (2013)[71]	Spain	IV	12 (6/6)	Knee	Culture-expanded BMSC	n/a	VAS WOMAC Lequesne severity index SF-36 Quality of Life Questionnnaire Poor Cartilage Index – MRI	12 mo

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Table II (*continued*)

First Author (Date of publication)	Country of origin	Level of evidence[56]	N* (Male/Female)	OA site	MSC Source/Type	Biologic adjuvant	Outcome measures	Follow-up length of time
Orozco (2014)[72]	Spain	IV	12 (6/6)	Knee	Culture-expanded BMSC	n/a	VAS WOMAC Lequesne severity index Poor Cartilage Index – MRI	2 yrs Follow-up Orozco (2013)[31]
Pak (2011)[94]	Korea	IV	2 (0/2)	Knee	SVF/ADSC	PRP, dexamethasone, hyaluronic acid	VAS Functional rating index RoM MRI evaluation of cartilage	3 mo
Pak (2013)[73]	Korea	IV	74 (X/X)	Hip ($n = 7$) Ankle ($n = 2$) Knee ($n = 74$)	SVF/ADSC	PRP, Hyaluronic acid	VAS for pain MRI – assessed for tumor formation	At least 12 mo
Pak (2016)[74]	Korea	IV	3 (1/2)	Knee	SVF/ADSC	ECM, Hyaluronic acid, PRP	VAS Functional rating Index RoM MRI cartilage assessment	18 wks
Park (2017)[75]	Korea	IV	7 (2/5)	Knee	Allogeneic, culture-expanded hUCB-MSCs	Hyaluronic acid hydrogel	ICRS grade VAS for pain IKDC Histological findings	7 yrs
Pintat (2017)[78]	France	IV	19 (10/9)	Patellofemoral	SVF/ADSC	PRP	WOMAC MRI – ICRS-like classification	12 mo
Russo (2017)[79]	Italy	IV	30 (21/9)	Knee	Microfragmented/ ADSC	n/a	VAS for pain KOOS IKDC - subjective Tegner Lysholm Knee	12 mo
Soler (2016)[80]	Spain	IV	15 (6/9)	Knee	Culture-expanded BMSC	n/a	VAS for pain WOMAC HAQ, pain subscale SF-36 Lequesne functional index MRI T2 mapping	12 mo
Turajane (2013)[32]	Thailand	IV	5 (1/4)	Knee	PBSC	Hyaluronic acid, GFA (PRP, hG-CSF)	WOMAC KOOS	6 mo
Bui (2014)[85]	Vietnam	IV	21 (X/X)	Knee	SVF/ADSC	PRP	VAS for pain Lysholm score MRI cartilage assessment	8.5 mo
Varma (2010)[81]	India	IV	50 (X/X)	Knee	BMAC/BMSC	n/a	VAS OAOS	6 mo
Wakitani (2011)[82]	Japan	IV	26 (X/X)	Knee	Culture-expanded BMSC	Collagen gel sheet	Adverse events: tumor development and infection	Mean: 75 mo
Wei (2011)[83]	USA	IV	23 (17/6)	Knee	BMAC/BMSC	PRP	WOMAC VAS for pain Patient Global Assessment 50 foot walk pain Physician Global Assessment	12 mo
Yokota (2017)[84]	Japan	IV	13 (4/22)†	Knee	SVF/ADSC	n/a	VAS for pain JKOM WOMAC	6 mo
Centeno (2008)[49]	USA	V	1(0/1)	Knee	Culture-expanded BMSC	Autologous whole-marrow, platelet lysate, dexamethasone	Modified VAS Functional Rating Index ROM MRI quantitative volume analysis	3 mo
Centeno (2008)[50]	USA	V	1(1/0)	Knee	Culture- expanded BMSC	Hyoluronate sodium, autologous whole-marrow, platelet lysate, dexamethasone	Modified VAS Functional Rating Index ROM MRI quantitative volume analysis	3 mo
Centeno (2008)[51]	USA	V	1 (1/0)	Knee	Culture- expanded BMSC	Autologous marrow-derived nucleated cells, platelet lysate, dexamethasone	Modified VAS Functional rating index ROM MRI quantitative volume analysis	6 mo

Table II (*continued*)

First Author (Date of publication)	Country of origin	Level of evidence[56]	N* (Male/Female)	OA site	MSC Source/Type	Biologic adjuvant	Outcome measures	Follow-up length of time
Mehrabani (2016)[69]	Iran	V	1 (0/1)	Knee	Culture-expanded BMSC	n/a	WOMAC VAS for pain Walking distance Time to gelling Patellar crepitus RoM MRI cartilage assessment	12mo
Pak (2017)[97]	Korea	V	1 (0/1)	Hip	SVF/ADSC	ECM, Hyaluronic acid, PRP	VAS for pain Functional rating index RoM MRI assessment of cartilage	20 wks

ADSC = adipose-derived stem cell; BMSC = bone-marrow stem cell; MSC = mesenchymal stem cell; OA = osteoarthritis; PBSC = peripheral blood stem cell; BMAC = bone marrow aspirate stem cell concentrate.
WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; MOAKS = MRI Osteoarthritis Knee Score; AOFAS = American Orthopedic Foot and Ankle Score; VAS = Visual Analogue Scale; ROM = Range of Motion; HHS = Harris Hip Score; FAOS = Foot and Ankle Outcome Score; ICOAP = intermittent and constant osteoarthritis pain; WORMS = Whole-Organ Magnetic Resonance Imaging Score; KSS = Knee Society Clinical Rating System; KOOS = Knee Injury and Osteoarthritis Outcome Score; IKDC = International Knee Documentation Committee; MOCART = Magnetic Resonance Observation of Cartilage Repair Tissue; ICRS = International Cartilage Repair Society; CMC = carpometacarpal; DASH = Disability of the Arm, Shoulder, and Hand scoring system; hUCB-MSCs = human umbilical cord blood-derived mesenchymal stem cells; SAS = Short Arthritis Assessment Scale; OARSI/OMERACT = Osteoarthritis Research Society International/Outcome Measures in Rheumatology response defined as 20% improvement of VAS and WOMAC from baseline; HAQ = Health Assessment Questionnaire; OAOS = Osteoarthritis Outcome Score; G-CSF = granulocyte colony stimulating factor; SVF = stromal vascular fraction; PRP = platelet-rich plasma; GFA = Growth Factor Addition; NPS = Numeric Pain Scale; GUG = Get-u and Go test; SCT = Stair Climbing Test; RPE = Rate of Perceived Exertion; dGEMRIC = delayed gadolinium-enhanced magnetic resonance imaging of cartilage; ECM = extracellular matrix; JKOM = Japanese Knee Osteoarthritis Measure; LEFS = Lower Extremity Functional Scale.
* N = number of patients in the treatment group.
† Based on number of knees treated.

Table III
Risk of Bias assessment using Cochrane's RoB 2.0 Scale for level I evidence studies and ROBINS-I scale for level II evidence studies

First Author (Date of publication)	Risk due to								
	Randomized process	Confounding	Participant selection	Intervention classification	Deviations from intended intervention	Missing data	Outcomes measurement	Selection of reported result	Overall
Garay-Mendoza (2017)[29]	Low				Low	Low	Low	Low	Low
Gupta (2016)[89]	Low				Low	Low	Low	Low	Low
Lamo-Espinosa (2016)[87]	Low				Low	Low	Low	Low	Low
Turajane (2017)[93]	Low				Low	Low	Low	Low	Low
Vega (2015)[94]	Low				Low	Low	Low	Low	Low
Centeno (2014)[88]		Moderate	Low	Low	Low	Moderate	Moderate	Low	Moderate
Jo (2014)[13]		Moderate	Low	Moderate	Low	Low	Moderate	Low	Moderate
Jo (2017)[90]		Moderate	Low	Moderate	Low	Moderate	Moderate	Low	Moderate
Koh (2014)[91]	Low				Low	Some concerns	Low	Low	Some concerns
Nguyen (2016)[30]		Low	Low	Low	Low	Low	Moderate	Moderate	Moderate
Pers (2016)[97]		Low	Low	Moderate	Moderate	Moderate	Moderate	Low	Moderate
Shapiro (2017)[92]	Low				Low	Low	Some concerns	Low	Some concerns
Wakitani (2002)[95]	Some concerns				Low	Some concerns	Some concerns	Some concerns	High
Wong (2013)[96]	Some concerns				Low	Low	Some concerns	Some concerns	High

NI = no information

All level I and II studies that measured WOMAC also saw improvements upon follow-up[13,29,30,87,89,90,93,94]. Lamo-Espinosa *et al.*[87] showed improved WOMAC scores in high-dose BMSC-treated patients than in the HA placebo group ($P < 0.01$). Garay-Mendoza *et al.*[29] reported similar improvement compared to acetaminophen placebo. Turajane *et al.*[93] also found significantly better WOMAC scores in PBSC-treated groups (WOMAC = 52 or 75) compared to the HA-placebo group (WOMAC = 126.8) at 12 months ($P < 0.001$). Two studies recorded improved WOMAC scores, but not when compared to placebo groups[89,94], and three studies exhibited improved WOMAC but lacked a placebo to compare to[13,30,90]. In one study, Garay-Mendoza *et al.*[29] demonstrated that BMSC treatment may lead to higher WOMAC scores (91.27 ± 9.45) compared to acetaminophen placebo (72.35 ± 17.37).

Few serious adverse events were found in level I and II evidence studies that measured safety[13,29,87,89,94,97]. Four studies found no serious events as a consequence to MSC-treatment, but patients noted mild pain and swelling post-treatment that was treated with ibuprofen[13,29,87,94]. Of the 288 patients included in level I and II evidence studies, these two patients were the only two with serious adverse events. Gupta *et al.*[89] recorded only one therapy-related serious adverse event of a synovial effusion, which was managed with overnight observation. Pers *et al.*[97] reported unstable angina in 1 patient with risk factors of hypertension and hyperlipidemia.

Radiologic measures were taken in five of the level I and II evidence studies with either MRI or X-ray imaging[13,87,90,91,94]. With X-ray, no change in joint space width[87] or no difference in femorotibial angle and weight bearing lines was noted[91]. MRIs have also

Table IV
Intervention details of the included level I and II evidence studies

First Author (Date of publication)	MSC type & extraction site	Biologic adjuvant	Injection procedure	Number of injected MSCs	Follow-up	Number of injections
Garay-Mendoza (2017)[29]	BMAC/BMSC: iliac crest	Outpatient SQ G-CSF x 3 days	Intra-articular injection of 10 mL concentrate without radiographic guidance	10 ml concentrate TNC: 302.2×10^7 Mononuclear: 67.33×10^7 $CD34^+$: 20.56×10^6	1 wk, 1, 6 mo	1
Gupta (2016)[89]	Allogeneic CE BMSC: from 3 healthy volunteers	PLASMALYTE-A Pre: Hydrocortisone and pheniramine maleate Post: Hyaluronic acid	Pre-medication of hydrocortisone and pheniramine maleate. Intra-articular injection without radiographic guidance followed by HA	4 dose levels: 25, 50, 75, 150×10^6	12 mo	1
Lamo-Espinosa (2016)[87]	CE BMSC: iliac crest	Hyaluronic acid	Intra-articular injection without radiographic guidance	Low-dose: 10×10^6 High-dose: 100×10^6	3, 6, 12 mo	2
Turajane (2017)[93]	PBSC	Hyaluronic acid, GFA (PRP, hG-CSF)	Arthroscopic microdrilling (group 1, 2) followed by intra-operative, intra-articular injection of: Group 1: PBSC, GFA, HA Group 2: PBSC, PRP, HA Group 3: HA only	3 ml PBSC Range TNC: 1.095 -1.276×10^6	1, 6, 12 mo	3
Vega (2015)[94]	Allogeneic culture-expanded BMSC: iliac crest	n/a	Intra-articular injection without radiographic guidance	40×10^6	8 days, 3, 6, 12 mo	1
Centeno (2014)[88]	CE BMSC: iliac crest	Platelet lysate	Intra-articular injection with radiographic and fluoroscopic guidance	5.76×10^6	3, 6, & 12 mo	1
Jo (2014)[13]	CE ADSC: SQ abdominal fat	n/a	Intra-articular injection with 3 mL saline	Low-dose: 10×10^6 Mid-dose: 50×10^6 High-dose: 100×10^6	6 mo	1
Jo (2017)[90]	CE ADSC: SQ abdominal fat	n/a	Intra-articular injection with 3 mL saline	Low-dose: 10×10^6 Mid-dose: 50×10^6 High-dose: 100×10^6	12, 24 mo	1
Koh (2014)[91]	SVF/ADSC: SQ buttocks	PRP	Intra-articular arthroscopic-guided injection followed by open-wedge HTO	120 ml of SVF Estimated 8.5% of 4.83×10^7 SVF cells (4.11×10^6)	Mean 24.2 ± 4.7 mo	1
Nguyen (2016)[30]	SVF/ADSC: SQ abdominal fat	PRP	Intra-articular injection with 5 ml SVF + PRP	10^7 SVF cells/ml	1, 6, 12, 18 mo	1
Pers (2016)[97]	CE ADSC: SQ abdominal fat	n/a	Intra-articular injection with ultrasound guidance	Low-dose: 2×10^6 Mid-dose: 10×10^6 High-dose: 50×10^6	6 mo	1
Shapiro (2017)[92]	BMAC/BMSC: iliac crest	Platelet-poor bone marrow plasma	Ultrasound guided intra-articular injection of 5 ml BMAC with 10 ml platelet-poor bone marrow plasma	Median of 3.4×10^4 MSCs and 4.62×10^6 hematopoietic stem cells	1 wk, 3 mo, 6 mo	1
Wakitani (2002)[95]	CE BMSC: iliac crest	Collagen gel sheet	HTO followed by collagen cell sheet with cells implanted	1.3×10^7	Mean: 16 months	1
Wong (2013)[96]	CE BMSC: iliac crest	Hyaluronic acid	HTO and microfracture followed 3 weeks later with intra-articular injection with 2 ml HA	$1.46 \pm 0.29 \times 10^6$	every 6 weeks for 6 mo, 1, 2 yrs	1 MSC 3 HA

ADSC = adipose-derived stem cell; BMSC = bone-marrow stem cell; MSC = mesenchymal stem cell; PBSC = peripheral blood stem cell; SQ = subcutaneous; HA = hyaluronic acid; CE = culture-expanded; TNC = total nucleated cells; HTO = high tibial osteotomy.

shown promising outcomes with a decrease in joint damage in two studies[13,87] and a decreased poor cartilage index (PCI) in another[94]. There is, however, some question of sustainability of radiologic outcomes. Jo et al. (2017) found that although at 6 months cartilage defect size decreased and cartilage volume increased, the change plateaued by the two-year follow-up[90].

Other measures less commonly used are noted in Table V including improvements in ICOAP[89,92], joint flexion and extension measurements[87], need for surgical intervention[93], Lequesne score[94], SF-12/36 life quality questionnaire[94,97], -100-to-+100 pain relief score[88], KSS[13,90], KOOS[90,91,97], Lysholm score[30,91,96], Kanamiya grading[91], Modified Outerbridge classification[30], activity level[92], HSS Knee Rating Scale[95], and second look arthroscopy and histology[95].

Discussion

Stem cell therapy appears to alleviate the symptoms of osteoarthritis and potentially halt cartilage damage. Although studies detailing the therapeutic effect of MSCs in osteoarthritic patients are limited in number and quality, the majority of available literature has reported positive results. The studies, however, are inconsistent in their methodology and few studies are levels I or II evidence. Over half (57%) of evidence available is level IV evidence which consists of therapeutic case series without comparative groups[39]. Nonetheless, analysis of the articles' results suggest an association between MSC therapy and OA symptomatic and radiologic improvement. There has been some conflicting evidence, however, in the longterm maintenance of positive results. In a two-

Table V
Outcome assessments of the included level I and II evidence studies

First Author (Date of publication)	Comparison groups	Outcomes measures	MSC group scores: Baseline vs Final F/U (x ± SD)	MSC-groups significant improvement from baseline	Comparison group scores: Baseline vs Final F/U	Significant improvement with comparison
Garay-Mendoza (2017)[45]	Acetaminophen 500 mg every 8 h for 6 months	VAS	5.27 ± 2.196 vs 0.92 ± 1.29		4.32 ± 2.35 vs 4.64 ± 2.43	Yes, $P < 0.0001$
		WOMAC*	62.61 ± 18.55 vs 91.73 ± 9.45		6.93 ± 17.89 vs 72.96 ± 15.04	Yes, $P < 0.0001$
		Safety	Swelling, pain, stiffness		Swelling, pain, stiffness	
Gupta (2016)[89]	Dose-escalation cohorts Placebo: injection of PLASMA-LYTE A	VAS	*Low dose:* 60.9 ± 19.7 vs 20.6 ± 17.3 *Low dose*: 73.7 ± 15.2 vs 45.3 ± 31.0 *High dose:* 57.4 ± 29.0 vs 37.1 ± N/A *High dose:* 46.6 ± 23.6 vs 43.6 ± N/A	No, $P > 0.05$ due to small sample size	*Placebo cohort 1:* 61.0 ± 23.8 vs 39.7 ± 28.3 *Placebo cohort 2:* 65.3 ± 12.2 vs 43.4 ± N/A	No, $P = 0.24$ No, $P = 0.11$
		ICOAP	*Low dose:* 45.7 ± 19.2 vs 21.4 ± 21.2 *Low dose:* 59.3 ± 21.7 vs 12.3 ± 27.4 *High dose:* 58.4 ± 20.7 vs N/A High dose: 46.4 ± 22.0 vs N/A	No, $P > 0.05$ due to small sample size	*Placebo cohort 1:* 49.3 ± 18.7 vs 7.5 ± 27.1 *Placebo cohort 2:* 54.8 ± 17.8 vs N/A	No, $P = 0.38$ No, $P = 0.54$
		WOMAC	*Low dose:* 1315.8 ± 444.8 vs 717.8 ± 503.8 *Low dose:* 1498.4 ± 407.4 vs 359.9 ± 786.4 *High dose:* 1470.6 ± 471.0 vs N/A *High dose:* 1388.1 ± 508.8 vs N/A	No, $P > 0.05$ due to small sample size	*Placebo cohort 1:* 1239.6 ± 472.2 vs 233.8 ± 641.9 *Placebo cohort 2:* 1392.0 ± 324.7 vs N/A	No, $P = 0.28$ No, $P = 0.9$
		Radiographic (WORMS)	*Low dose:* 67.0 ± 19.2 vs 66.1 ± 19.2 *Low dose:* 78.8 ± 40.9 vs 78.0 ± 41.1 *High dose:* 71.3 ± 21.4 vs 67.0 ± 15.7 *High dose:* 70.8 ± 14.7 vs 72.3 ± 15.2	N/A	*Placebo cohort 1:* 76.5 ± 23.5 vs 74.9 ± 22.5 *Placebo cohort 2:* 70.8 ± 14.7 vs 72.3 ± 15.3	No, $P = 0.5310$ No, $P = 0.0609$
		Safety	Pain and swelling One serious event: synovial effusion	N/A	Pain and swelling	N/A
Lamo-Espinosa (2016)[87]	Dose escalation cohorts Placebo: HA alone	VAS (IQR)	*Low dose:* 7 (5,8) vs 2 (1,3) *High dose:* 6(4,8) vs 2 (0,4)	N/A	5 (3,7) vs 4 (3,5)	*With low dose cohort:* Yes, $P = 0.005$ *With high dose cohort:* Yes, $P < 0.009$
		WOMAC	*Low dose:* 37 (11,37) vs 21.5 (15,26) *High dose:* 28 (16,34) vs 16.5 (12,19)	No, $P > 0.05$ Yes, $P < 0.01$	29 (19,38) vs 13.5 (8,33)	N/A
		Radiographic (WORMS, X-Ray)	MRI (WORMS): decreased joint damage X-Ray: no change in joint space width	N/A	MRI (WORMS): no change in joint damage X-Ray: reduction in joint space width	N/A
		Knee Flexion and Extension Measurements	*Flexion measurement:* *Low dose:* 116 (110,116) vs 119 (116,122) *High dose:* 110 (110,117) vs 118(116, 122) *Extension measurement:* *Low dose:* 176 (173,180) vs 180 (176, 180) *High dose:* 177 (174,180) vs 180 (180,180)	Yes, $P < 0.05$ Yes, $P < 0.05$ Yes, $P < 0.05$ Yes, $P < 0.05$	*Flexion*: 118 (114,120) vs 118 (115,118) *Extension:* 180 (176, 180) vs 179 (175, 180)	N/A

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Table V (*continued*)

First Author (Date of publication)	Comparison groups	Outcomes measures	MSC group scores: Baseline vs Final F/U (x ± SD)	MSC-groups significant improvement from baseline	Comparison group scores: Baseline vs Final F/U	Significant improvement with comparison	
		Safety	No adverse events besides mild pain	N/A	No adverse events besides mild pain	N/A	
Turajane (2017)[93]		*Cohort 1:* PBSCs, HA, PRP, hG-CSF, and microdrilling treatment *Cohort 2:* like cohort 1 but without hG-CSF Placebo: HA alone	Need for surgical intervention at 12 months	*Cohort 1*:0 patients need joint replacement *Cohort 2*:0 patients need joint replacement	N/A	3 need joint replacement	Yes, $P < 0.033$
			WOMAC	*Cohort 1:* 218.5 vs 52 *Cohort 2:* 212.2 vs 75	Yes, $P < 0.0001$ Yes, $P < 0.0001$	215.3 vs 126.8	*With cohort 1:* Yes, $P < 0.001$ *With cohort 2:* Yes, $P < 0.001$
Vega (2015)[94]	Placebo: HA alone	VAS[SE]	54 ± 7 vs 33 ± 6	N/A	64 ± 7 vs 51 ± 8	Yes, $P < 0.005$	
		WOMAC[SE]	41 ± 3 vs 28 ± 5	N/A	45 ± 3 vs 41 ± 6	Yes, $P < 0.005$	
		Lequesne score[SE]	39 ± 4 vs 30 ± 3	N/A	45 ± 4 vs 42 ± 5	Yes, $P < 0.005$	
		SF-12 PCS	40 ± 9 vs 45 ± 11	No, $P > 0.05$	35 ± 8 vs 40 ± 8	No, $P > 0.05$	
		SF-12 MCS	54 ± 10 vs 51 ± 12	No, $P > 0.05$	49 ± 9 vs 47 ± 11	No, $P > 0.05$	
		MRI (PCI)	Decreased significantly by 1 year	Yes, $P < 0.05$	Does not drop significantly by 1 year	No, $P > 0.05$	
		Safety	Inflammation during first 7 days	N/A	Inflammation during first 7 days	N/A	
Centeno (2014)[88]	Untreated procedure candidates (No placebo)	−100% to +100% pain relief scale	60% improvement		19 % improvement	Yes, $P = 0.03$	
		VAS	63% improvement (5.2 vs 2.0)				
Jo (2014)[13]	Dose-escalation cohorts (No placebo)	WOMAC[SE]	*Low dose:* 43.4 ± 12.7 vs 25.3 ± 19.5 *Mid-dose:* 69.0 ± 5.9 vs 48.5 ± 11.0 *High dose:* 54.2 ± 5.2 vs 32.8 ± 6.3	No, $P = 0.339$ No, $P = 0.391$ Yes, $P = 0.003$	N/A	N/A	
		Safety	No treatment-related adverse events	N/A	N/A	N/A	
		VAS	Low dose: 70.0 ± 10.0 vs 48.3 ± 14.8 *Mid-dose*: 78.3 ± 1.7 vs 67.5 ± 11.5 *High dose*: 79.6 ± 2.2 vs 44.2 ± 6.3	No, $P = 0.069$ No, $P = 0.486$ Yes, $P = 0.000$	N/A	N/A	
		KSS Knee score	*Low dose:* 41.3 ± 6.8 vs 79.0 ± 12.5	Yes, $P = 0.025$	N/A	N/A	
		KSS Function score	*Mid-dose:* 35.3 ± 9.8 vs 47.3 ± 6.8 *High dose:* 47.2 ± 2.6 vs 71.0 ± 4.4 *Low dose:* 60.0 ± 5.8 vs 83.3 ± 8.8 *Mid-dose:* 56.7 ± 6.7 vs 70.0 ± 7.6 *High dose:* 70.8 ± 2.6 vs 77.5 ± 2.5	No, $P = 0.324$ Yes, $P = 0.000$ Yes, $P = 0.020$ No, $P = 0.333$ No, $P = 0.120$	N/A	N/A	
		Radiographic: depth of cartilage defect, Radiographic: articular cartilage volume)	*High dose cohort,* (at medial femoral and tibial condyles): 497.9 ± 29.7 vs 297.9 ± 51.2 333.2 ± 51.2 vs 170.6 ± 48.2 *High dose cohort,* (at medial femoral and tibial condyles): 3313.7 ± 304.1 vs 3780.6 ± 284.4 1157.5 ± 145.8 vs 1407.7 ± 150.5	Yes, $P < .05$ Yes, $P < 0.05$	N/A N/A	N/A N/A	
Jo (2017)[93]	Dose-escalation cohorts (No placebo)	WOMAC	*Low dose:* 43.3 ± 12.7 vs 17.0 ± 9.8 *Mid-dose:* 69.0 ± 5.9 vs 25.1 ± 11.0 *High dose:* 54.2 ± 5.2 vs 19.0 ± 5.5	No, $P = 0.083$ No, $P = 0.210$ Yes, $P < 0.001$	N/A	N/A	

		VAS	*Low dose:* 70.0 ± 10.0 vs 40.0 ± 15.3 *Mid-dose:* 78.3 ± 1.7 vs 66.0 ± 14.7 *Low dose:* 79.6 ± 2.2 vs 45.8 ± 8.1	Yes, $P = 0.035$ No, $P = 0.601$ Yes, $P = 0.002$	N/A	N/A	
		KSS Knee score KSS Function score		*Low dose:* 41.3 ± 6.8 vs 71.0 ± 12.1 *Mid-dose* 35.3 ± 9.8 vs 70.8 ± 12.8 *High dose:* 47.2 ± 2.6 vs 79.3 ± 4.7 *Low dose:* 60.0 ± 5.8 vs 86.7 ± 3.3 *Mid-dose:* 56.7 ± 6.7 vs 73.3 ± 11. *High dose:* 70.8 ± 2.6 vs 83.3 ± 3.8	Yes, $P = 0.031$ No, $P = 0.241$ Yes, $P =< 0.001$ Yes. $P = 0.015$ No, $P = 0.439$ Yes, $P = 0.026$ But, plateaus at 1 year F/U	N/A N/A	N/A N/A
		KOOS pain score KOOS symptom score KOOS activities of daily living score	*Low dose:* 49.1 ± 4.0 vs 69.4 ± 12.7 *Mid-dose:* 30.6 ± 12.1 vs 61.0 ± 9.9 *High dose:* 32.6 ± 4.1 vs 76.4 ± 5.4 *Low dose:* 61.9 ± 7.2 vs 72.6 ± 5.2 *Mid-dose:* 39.3 ± 16.4 vs 76.9 ± 10.5 *High dose:* 48.5 ± 5.3 vs 72.9 ± 5.2 *Low dose:* 58.8 ± 10.0 vs 81.9 ± 9.7 *Mid-dose:* 22.5 ± 6.0 vs 73.1 ± 12.7 *High dose:* 28.6 ± 3.6 vs 33.9 ± 3.0	No, $P = 0.148$ No, $P = 0.220$ Yes, $P < 0.001$ Yes, $P = 0.035$ No, $P = 0.214$ Yes, $P = 0.003$ Yes, $P = 0.001$ No, $P = 0.237$ Yes, $P < 0.001$	N/A N/A N/A	N/A N/A N/A	
		Radiographic (MRI)	No significant change in joint space width, mechanical or anatomic axis. *Low dose:* no significant change in cartilage defect *High dose:* regenerated cartilage 6 months. not 2 years	Yes, $P < 0.05$†	N/A	N/A	
Koh (2014)[91]	PRP alone	VAS	44.3 ± 5.7 vs 10.2 ± 5.7	N/A	45.4 ± 7.1 vs 16.2 ± 4.6	Yes, $P < 0.001$	
		KOOS pain scale KOOS symptom scale Lysholm score	81.2 ± 6.9 vs N/A 82.8 7.2 vs N/A 55.7 ± 11.5 vs 84.7 ± 16.2	N/A N/A	74.0 ± 5.7 75.4 ± 8.5 56.7 ± 12.2 vs 80.6 ± 13.5	Yes, $P < 0.001$ Yes, $P = 0.006$ No, $P = 0.357$	
		Radiographic (FTA and WBL)	Varus 3.4 ± 3.0 vs Valgus 8.7 ± 2.3 17.7 ± 7.3 vs 61.1 ± 3.4	N/A	Varus 2.8 ± 1.7 vs Valgus 9.8 ± 2.4 16.1 ± 5.7 vs 60.3 ± 3.0	No, $P > 0.05$ No, $P > 0.05$	
Nguyen (2016)[30]	Arthroscopic microfracture alone	WOMAC	42.87 ± 16.29 vs 17.33 ± 14.91	N/A	47.37 ± 17.13 vs 37.08 ± 21.45	Yes, $P < 0.05$	
		Lysolm score	53.47 ± 14.56 vs 84.73 ± 19.54	N/A	64.13 ± 10.19 vs 65.17 ± 14.74	Yes, $P < 0.05$	
		VAS for pain	1.60 ± 0.83 vs 3.47 ± 0.74	Yes, $P < 0.05$	2.67 6 0.62 vs 1.40 6 0.51	Yes, $P < 0.05$	
		Modified Outerbridge classification	3.33 ± 0.97 vs 2.93 ± 0.88	N/A	2.67 ± 1.35 vs 4.02 ± 1.08	No, $P > 0.05$ Note: scores increase in placebo, decrease if treated	
Pers (2016)[97]	Dose-escalation cohorts (No placebo)	Safety	Only one severe adverse event (UA in a patient with multiple risk factors)	N/A	N/A	N/A	
		VAS	*Low dose:* 77 ± 15.7 vs ± 35.8 ± 13.3 *Mid-dose:* 63.7 ± 20.5 vs 36.7 ± 11.9 *High dose*: 43.7 ± 25.4 vs 24 ± 17.1	Yes, $P < 0.05$ No, $P = 0.09$ No, $P = 0.54$	N/A	N/A	
		WOMAC	*Low dose:* 60.7 ± 18.6 vs 27.6 ± 8.9 *Mid-dose:* 47.2 ± 14.7 vs 24.3 ± 9.1 High dose: 38.8 ± 27.3 vs 6.2 ± 16.0	Yes, $P < 0.001$ No, $P = 0.054$ No, $P = 0.38$	N/A	N/A	
		KOOS	*Low dose:* 34 ± 15 vs 65.8 ± 9.1 *Mid-dose:* 42 ± 9 vs 59.2 ± 6.5 *High dose:* 45.2 ± 13.6 vs 65.2 ± 13.1	Yes, $P < 0.01$ Yes, $P < 0.05$ No, $P = 0.32$	N/A	N/A	

(*continued on next page*)

Table V (*continued*)

First Author (Date of publication)	Comparison groups	Outcomes measures	MSC group scores: Baseline vs Final F/U (x ± SD)	MSC-groups significant improvement from baseline	Comparison group scores: Baseline vs Final F/U	Significant improvement with comparison
		SF-36 PCS	*Low dose:* 30.9 ± 8.2 vs 39.1 ± 4.6	No, $P = 0.33$	N/A	N/A
		SF-36 MCS	*Mid-dose:* 29.9 ± 6.2 vs 35.3 ± 4.0	No, $P = 0.42$	N/A	N/A
			High dose: 35.7 ± 10.6 vs 37.6 ± 6.8	No, $P = 0.98$		
			Low dose: 55.9 ± 8.3 vs 51.9 ± 3.8	No, $P = 0.60$		
			Mid-dose: 51.9 ± 10.2 vs 55.1 ± 5.8	No, $P = 0.91$		
			High dose: 53.6 ± 7.8 vs 54.1 ± 6.6	No, $P = 0.99$		
Shapiro (2017)[92]	Saline into each patient's contralateral knee. Patient blinded to knee with treatment vs placebo.	VAS for pain	3.1 vs 1.5	Yes, $P = 0.001$	2.9 vs 0.8	No, $P = 0.44$
		ICOAP	32 vs 16	Yes, $P = 0.0005$	32 vs 9	No, $P = 0.54$
		Activity level	*No/mild limits:* 6 vs 15	Yes, $P = 0.0003$	No/mild limits: 8 vs 17	No, $P = 0.51$
			Moderate limits: 13 vs 9		Moderate limits: 11 vs 5	
			Severe/extreme limits: 6 vs 1		*Severe/extreme limits:* 6 vs 3	
Wakitani (2002)[95]	Cell-free collagen gel-sheet implantation	HSS Knee Rating Scale	65.0 ± 6.7 vs 81.3 ± 8.6	Yes, $P = 0.0029$	66.3 ± 10.5 vs 79.2 ± 8.7	No, $P > 0.05$
		Arthroscopic/histologic cartilage evaluation	9.8 ± 2.0 vs 15.4 ± 1.4		7.5 ± 2.2 vs 10.0 ± 6.1 8.0 ± 0.9 vs 11.3 ± 2.3	Yes, $P < 0.05$
Wong (2013)[96]	HTO + HA alone	Lysholm score[i]	41.9 ± 19.2 vs N/A Improvement of 7.61	Yes, $P = 0.016$	50.4 ± 23.0 vs N/A	Yes, $P = 0.016$
		IKDC[i]	33.9 ± 11.4 vs N/A Improvement of 7.65	Yes, $P = 0.001$	36.0 ± 13.7 vs N/A	Yes, $P = 0.001$
		Radiographic (MOCART)	62.32 ± 17.56		43.21 ± 13.55	Yes, $P < 0.001$

F/U = follow-up; VAS = visual analog scale; ICOAP = intermittent and constant osteoarthritis pain; WOMAC = Western Ontario and McMaster Universities Osteoarthritis index; WORMS = whole organ magnetic resonance imaging score; MSC = mesenchymal stem cells; SD/SE = standard deviation/standard error; HA = hyaluronic acid; PBSC = peripheral blood stem cell; PRP = platelet-rich plasm; hG-CSF = granulocyte colony stimulating factor; SF-12/36 PCS = standard form 12/36 physical component score; SF-12/36 MCS = standard form 12/36 mental component score; PCI = poor cartilage index; KSS = Knee Society clinical rating system score; KOOS = Knee injury and osteoarthritis outcome score; MRI = magnetic resonance imaging; FTA = femotibial angle; WBL = weight-bearing line; HSS = Hospital for Special Surgery; IKDC = international knee documentation committee score; MOCART = magnetic resonance observation of cartilage repair tissue score; UA = unstable angina; HTO = high tibial osteotomy; N/A = not available; IQR = interquartile range.

[SE] study reported standard error instead of standard deviation for this outcome measure.

[*] This study considered at WOMAC scale of 0–100, with a score of 100 indicating the best outcomes.

[†] At medial and lateral femoral and tibial condyles and at 6 months, at medial femoral and lateral tibial condyle at 2 years.

year follow-up, Jo *et al.*[77] found that although WOMAC, VAS, KSS and KOOS improved from baseline, these scores plateaued or decreased after one year. To the contrary, Nguyen *et al.*[44] looked at WOMAC, Lysholm score, and VAS and found that both treatment and placebo groups significantly improved from baseline ($P < 0.05$), but it was not until 18 months that the treated group had significantly improved scores compared to placebo ($P < 0.05$). This supports the need for studies that assess longer term clinical outcomes in order to better understand the intervention's sustainability. This also draws attention to the need for protocol consistency since it is difficult to formulate conclusions from these longterm studies when different forms of MSC administration are used, as demonstrated by these examples, respectively[44,77].

MSC therapy caused few adverse effects in studies that investigated treatment safety. Two serious adverse events were recorded in the levels I and II evidence including a synovial effusion requiring overnight observation[89] and unstable angina in a patient with multiple risk factors three months after injection.[97] Other adverse events recorded included pain and swelling. Vega *et al.*[94] found 50–60% of all patients, both treatment and control group, experienced inflammation and swelling post-injection procedure. This highlights the possibility of adverse events being due to injections in general, vs the stem cells themselves. As previously mentioned, this is supported by systematic reviews for the safety of therapeutic uses of MSCs. The most common adverse events noted in these studies have been pain and swelling[15,16] with several studies rejecting a previous concern for increased tumor risk[16,74,82].

The methodology of the included studies was widely variable. This suggests that studies have not been replicated to validate results, which limited our ability to conduct meta-analysis. There is no consensus as to which MSC type is most effective at treating OA. More recently, one-step preparation of MSC-containing product including SVF, BMAC or microfragmented adipose tissue adds to this variability. Even within the levels I and II evidence articles, there was no dominant stem cell type; the research spanned ADSCs (5 study), BMSCs (8 studies), and PBSCs (1 study), and, within each MSC type, procedural variability remains. Amongst the levels I and II evidence, three studies used radiographic guidance[88,92,97], one used arthroscopic guidance[85], one was implanted in an open procedure[95], while nine reported neither. Three studies[93,95,96] were completed in conjunction with a surgical procedure. There is also variability in adjuvants, but the most common used are PRP ($n = 20$), platelet lysate ($n = 8$), and hyaluronic acid ($n = 10$).

Besides the lack of consistent methodologies, this study elucidates the scarcity of quality evidence. The majority (57%) of included clinical studies were level IV case series, an additional 11% were level III retrospective cohort studies and 8% were level V single patient case reports. Furthermore, risk of bias is a concern amongst the level II evidence articles (15% of included studies), with all at moderate/some concerns or high risk of bias, indicating the potential for underestimation or overestimation of results. These data demonstrate the need for higher quality evidence regarding MSC treatment for OA. The literature needs more level II prospective cohort studies designed to minimize risk of bias and, importantly, more level I randomized controlled trials to effectively evaluate the MSC treatment. All current level I evidence articles were categorized as low risk of bias, which is promising for future publication of well-designed studies, though consensus must still be reached on proper methodology.

There are several limitations to this study. Many studies in foreign languages were excluded due to our inability to analyze them. Another limitation lies in our choice of evidence levels and risk of bias. Marx, Wilson, Swiontkowski (2015) allows authors to use their professional judgment to grade levels of evidence[39], as do the tools for assessing risk of bias[26,58]. Thus, there is flexibility in selecting levels of evidence and risk of bias, though the authors collaborated to arrive at conclusions. Additionally, we recognize the need for consistency between studies, including but not limited to MSC type/implanted or injected material, number of cells injected/implanted, use of biologic adjuvants and outcome measures. With this, we also recognize that the reported outcome measures exist without a true understanding of the mechnanism of action of MSCs. This makes it difficult for us to truly understand results. For example, after finding improvement in treatment groups using each patient's contralateral knee as a control, Shapiro *et al.*[92] speculated several explanations for their results including the possibility of systemically mediated effects of BMAC, paracrine signaling mechanisms, chondrogenic potential and even the interaction of other cells in the concentrate. The answer was not found and needs further study. We are therefore unable to propose guidelines of stem cell therapy extraction and injection methods based on the available evidence. Lastly, we recognize that active stem cell therapy clinical trials found through clinicaltrials.gov were not included in our analysis of the literature. Mamidi *et al.*[98] reviewed the obstacles faced by clinical trials and found 40 clinical trials registered in 19 different countries. These studies will hopefully be a source of new and more reliable evidence.

The Food and Drug Administration (FDA) regulates the use of adult stem cells. In 2006, the FDA adopted 21 CFR 1271, which modified its jurisdiction over human cells and tissues to include any "transfer into *a* human recipient[99]." Previously, the code was specified transfer "into *another* human," excluding autologous cells[100,101]. Since then, cells that are more than "minimally manipulated," even if they are intended for autologous use, are subject to similar regulations as manufactured drugs[100,101]. Therefore, higher quality evidence is not only needed to convince physicians, but the FDA as well, of the safety and efficacy of MSCs. High level, quality evidence for MSC therapy would allow the FDA and physicians to more confidently provide patients with alternative, minimally invasive treatment options that may significantly slow disease progression.

The need to further investigate MSC therapy for OA comes from the quality of the existing treatment options. OA treatment thus far relies on conservative management and invasive joint replacement surgeries[5–8]. Stem cell therapy is a rapidly evolving treatment for osteoarthritis that has been used despite proper evidence to support its application. Few high level of evidence articles have been published with respect to this matter. Although MSC safety has been shown, the literature has no cohesive picture regarding the proper collection and administration of stem cells. We have reported a general link between MSC therapy and OA symptomatic improvement, but the data is limited by study quality. A well-designed randomized controlled trial with reproducible methodology is needed to further evaluate how different derivatives of MSCs such as BMSCs, ASCs, and PBSCs affect OA as well as MSC-containing products such as SVF or BMAC.

Contributions

David S. Jevotovsky, BA: This author was responsible for the design of the study as well as acquisition, analysis and interpretation of data. He drafted, revised, and was part of the final approval process.

Allyson R. Alfonso, BS, BA: This author was responsible for the conception of the study, elaboration of study design, acquisition of data, analysis and interpretation of the data. She revised the article and was part of the final approval process.

Thomas A Einhorn, MD: This author was part of the conception and design of the study. He helped revise the article for important intellectual content and was part of the final approval process.

Ernest S. Chiu, MD: This author is the principal investigator for this work. He was responsible for design of study as well as analysis and interpretation of data. He also contributed to revision of the manuscript and final approval.

Competing interest statement

Dr. Einhorn reports personal fees from Agnovos, personal fees from Pluristem, personal fees from Harvest Technologies, outside the submitted work. In addition, Dr. Einhorn has a patent MyDigitalRx pending and is an investor with HealthpointCapital, a private equity firm in the orthopaedic space. The other authors have no conflicts of interests to report.

Role of the funding source

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