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Improved outcomes after mesenchymal stem cells injections for knee osteoarthritis: results at 12-months follow-up: a systematic review of the literature

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Abstract

Purpose According to the World Health organization (WHO), more than 10% in people older than 60 years suffer from osteoarthritis (OA). Over the last years, there has been an increased interest around regenerative medicine, especially regarding stem cell treatments and related applications. We hypothesize that stem cell therapies can represent a feasible option for idiopathic knee OA, delaying or even avoiding the joint replacement. To emphasize the potential of percutaneous injections of mesenchymal stem cells for knee OA, a comprehensive systematic review of the literature was conducted.

Material and methods Two independent authors (FM, GC) performed the literature search. This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA). The main databases were accessed: Pubmed, Embase, Google Scholar, Cochrane Systematic Reviews, Scopus, AMED. For this systematic review, all articles treating percutaneous injections of mesenchymal stem cells for knee OA were considered. Because of the rapid advancements promoted by the scientific progress on stem cell expansion and processing, only articles published within the last five years were included. Solely articles reporting the outcomes of interest across 6- and 12-month follow-up were recruited for eligibility. We included only studies reporting quantitative data under the outcomes of interest. We referred for the quality assessment to the Coleman Methodology Score (CMS). The statistical analysis was performed with Review Manager Software 5.3 (The Nordic Cochrane Centre, Copenhagen).

Results A total of 18 studies were enrolled in the present study, comprising 1069 treated knees. The mean age of the samples was 57.39 ± 7.37 years. 72% of the included studies harvested the stem cells from the iliac crest (bone marrow-derived MSCs), the remaining 28% from the adipose tissue (adipose-derived MSCs). The mean visual analogic scale improved from 18.37 to 30.98 and 36.91 at 6- and 12-month follow-up, respectively. The mean WOMAC score improved from 25.66 to 25.23 and 15.60 at 6- and 12-month follow-up, respectively. The mean walking distance improved from 71.90 to 152.22 and 316.72 at 6- and 12-month follow-up, respectively. The mean Lequesne scale improved from 33.76 to 12.90 at 12-month follow-up. The KOOS score improved from 41.07 to 8.47% and 18.94 at 6- and 12-month follow-up. All the KOOS subscales improved significantly from the baseline. A total of 136 (12.7%) local complications were detected.

Conclusion According to the current evidences and the main findings of this systematic review, we reported that MSC infiltrations for knee OA can represent a feasible option, leading to an overall remarkable improvement of all clinical and functional considered outcomes, regardless of the cell source. Patients treated at earlier-degeneration stages reported statistically significant greater outcomes. The pain and function scores were improved considerably, thus, leading to a significant improvement of patient participation in recreational activities and quality of life.

Keywords Osteoarthritis · Knee · Mesenchymal stem cells · Infiltrations

Introduction

According to the World Health organization (WHO), more than 10% of people older than 60 years suffer from osteoarthritis (OA) [1]. The first approach for symptomatic

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knee OA is represented by analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs). These drugs lead to gastrointestinal and cardiovascular adverse events in the long run [2]. Furthermore, they are not able to stop the OA cascade, or even to guarantee a long-term pain relief [3]. Platelet-rich plasma, hyaluronic, corticosteroids, and local anaesthetic injections represent additional options for early stage joint degeneration; however, the long-term results are poor and lack professional consensus [4–6]. Knee arthroplasties (partial or total) remain the gold standard treatments for end stage OA, reporting high clinical and functional outcomes and being cost-effective [7, 8]. On the downside, they expose the patients to the risk of several complications and further revision surgeries [9].

Regenerative medicine, especially stem cell therapies, attracts more attention from the scientific communities than ever by achieving promising results [10, 11]. From a theoretical point of view, stem cells can be committed in every cell lineage in order to replace and repair damaged human tissues [12, 13]. Stem cell therapies are closely connected/linked to the progress of other disciplines, such as molecular biology, which is essential to understand signalling pathways, proliferations, differentiations and expansion patterns [14, 15].

We hypothesize that stem cell therapies may represent feasible options for idiopathic knee OA, delaying joint replacement. Several studies have attempted to delineate these therapies, but there is no recent study to have reviewed the latest evidence, indications, and outcomes. This review aims to update the current state of research concerning the potential of percutaneous injections of mesenchymal stem cells for knee OA. We tried to clarify the current indications and to summarize biological pathways supporting these infiltrations, along with the outcomes and criteria of patient selection.

Materials and methods

Search strategy

Two independent authors (FM, GC) performed the literature search. This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA) [16]. A preliminary protocol was carried out to guide the initial research:

(a) Population: knee OA;
(b) Intervention: percutaneous mesenchymal stem cells injection;
(c) Outcomes: clinical and functional scores, further complications.

Data extraction

The main databases were accessed in December 2018: Pubmed, Embase, Google Scholar, Cochrane Systematic Reviews, Scopus, AMED. The following keywords were used in combination: knee osteoarthritis and/ or degeneration combined with mesenchymal stem cells (MSC) and/ or bone marrow-derived or adipose-derived or peripheral blood-derived combined with injection and/ or percutaneous. If the title matched, the abstract was carefully examined and, if suitable, the full-text was accessed. Furthermore, the bibliographies of all relevant studies were evaluated for inclusion as well.

Eligibility criteria

Two independent authors (FM, GC) screened the articles resulting from the search for suitability/eligibility. For this systematic review, all articles treating percutaneous injections of mesenchymal stem cells for knee OA were considered. In accordance with the authors' capabilities, articles in English, German, Italian, Spanish, and French were considered. Correspondent to the Oxford Centre of Evidence-Based Medicine [17], levels of evidence I, II, and III were included. Due to rapid advancements promoted by the scientific progress on stem cells expansion and processing, only articles published in the last 5 years were included. Articles discussing infiltrations with proteins, collagens, fibrins or other components of the extracellular matrix were excluded. Studies considering infiltrations with chondrocytes, osteocytes, synoviocytes, erythrocytes of platelets or another committed lineage were rejected. Studies performing infiltration of bone marrow aspirate (BMA) or platelet-rich plasma (RPR) were excluded. Studies addressing allogeneic or heterogenic transplants, along with studies discussing embryonal or umbilical cord stem cells were excluded. Moreover, studies involving totipotent as pluripotent and other less committed stem lineages were excluded. Additionally, papers treating patients with previous or planned knee surgery, along with studies infiltrating cells under arthroscopic guidance and studies treating patients suffering from acute traumas, chondropathies, focal or multiple chondral defects were rejected. Solely articles reporting the outcomes of interest across 6- and 12-month follow-up were regarded as suitable. We enrolled studies treating patients suffering from OA with percutaneous injections of mesenchymal stem cells only. Similarly, they were required to report quantitative data under the outcomes of interest.

Outcomes of interest

Two independent authors (FM, GC) performed the data collection. For each article, the following data were extracted: author, year, type of study, mean age and follow-up, number

of patients, control group, cell source, dose injected, inclusion and exclusion criteria, and further complications. The following scores were considered: visual analogic scale (VAS), WOMAC [18], Knee injury and Osteoarthritis Outcome Score (KOOS) and related subscales [19], Walking distance (meters), and Lequensne index [20]. We divided all studies into two groups, depending on the length of the follow-ups of either 6 or 12 months. The following subgroup analyses was performed: according to the donor-tissue source (adipose- versus bone marrow-derived MSCs) and according to the Kellgren and Lawrence scale (grade II to III versus II to IV).

Methodological quality assessment

For the quality assessment, we referred to the Coleman Methodology Score (CMS). The values related to each article were assessed independently by two authors (FM, GC). This score evaluates the included studies under different points of view: number of enrolled patients, mean follow-up, type of approach and study, description of diagnosis, surgical technique and post-operative rehabilitation. Furthermore, the criteria, the procedures, and the selection process are evaluated. For final evaluation, the CMS results in a value ranging from 0 (poor) to 100 (excellent).

Statistical analysis

The statistical analysis was performed with Review Manager Software 5.3 (The Nordic Cochrane Centre, Copenhagen). To evaluate continuous data and related overall effect estimate (EE), the arithmetic mean and standard deviation (SD) were calculated. The inverse variance (IV) statistical method with the mean difference was used to evaluate the level of improvement across the follow-ups. The confidence interval (CI) was set to 95% for the entire comparison. Both χ^2 and I^2 (Higgins) tests were performed to assess the heterogeneity. A fixed effect method was initially used. If χ^2 resulted in $P > 0.5$ and the $I^2 > 50\%$, the comparison was analysed under a random effect analysis method. Values of $P > 0.5$ were considered statistically significant.

Results

Search result

The literature research resulted in 3512 articles. After removing duplicates, 3288 articles in total were screened for inclusion. A total of 2474 was excluded because they did not match the eligibility criteria. Another 537 were excluded due to lack of data in regard to the outcomes of interest. Further, 239 articles were excluded because of insufficient quantitative data. An additional 13 studies were rejected due to poor quality or ambiguous results. 7 articles were excluded because no data was reported regarding the mentioned follow-up periods (6 and/or 12 months). This left 18 articles for this systematic review. The literature flow-chart is shown in Fig. 1.

Methodological quality assessment

The CMS scored 59.8 ± 7.96 (good quality). Discussing and contextualizing this result are immensely important, since the CMS was negatively influenced by the lack of randomization, which was merely applied to 11% of the included studies. However, only one included study was retrospective, while the other 83% were prospective, representing the improved methodological quality of this work. In consequence of the inept blinding and randomization of the abovementioned treatments, it becomes apparent that the score underestimates their overall quality. In conclusion, we validated the superior quality of the methodological assessment. The results of the CMS of each study are shown in Table 1.

Patients demographic

A total of 1069 knees were enrolled in the present study. The mean age of the samples was 57.39 ± 7.37 years. Three studies took advantage of a control group. 72% of all studies harvested the stem cells from the iliac crest (bone marrow-derived MSCs), whereas 28% harvested from the adipose tissue (adipose-derived MSCs). The mean volume injected into the joint was 39.01 ml. The demographic baseline of the studied groups is shown in Table 1.

Outcomes of interest

The mean visual analogic scale improved from a baseline of 55.20 ± 18.37 to 30.98 and 36.91 at 6- and 12-month follow-up, respectively. The mean WOMAC score improved from a baseline of 25.66 ± 15.10 to 25.23 and 15.60 at 6- and 12-month follow-up, respectively. Likewise, the mean walking distance improved from a baseline of 71.90 ± 28.41 m to 152.22 and 316.72 m at 6- and 12-month follow-up, respectively. The mean Lequesne scale improved from a baseline of 33.76 ± 19.72 to 12.90 at 12-month follow-up. The KOOS score improved from a baseline of 41.07 ± 12.17 to 8.47 and 18.94 at 6- and 12-month follow-up. In addition, all the KOOS subscales improved significantly from the baseline to both 6- and 12-month follow-up. The overall results of the comparison are shown in Table 2.

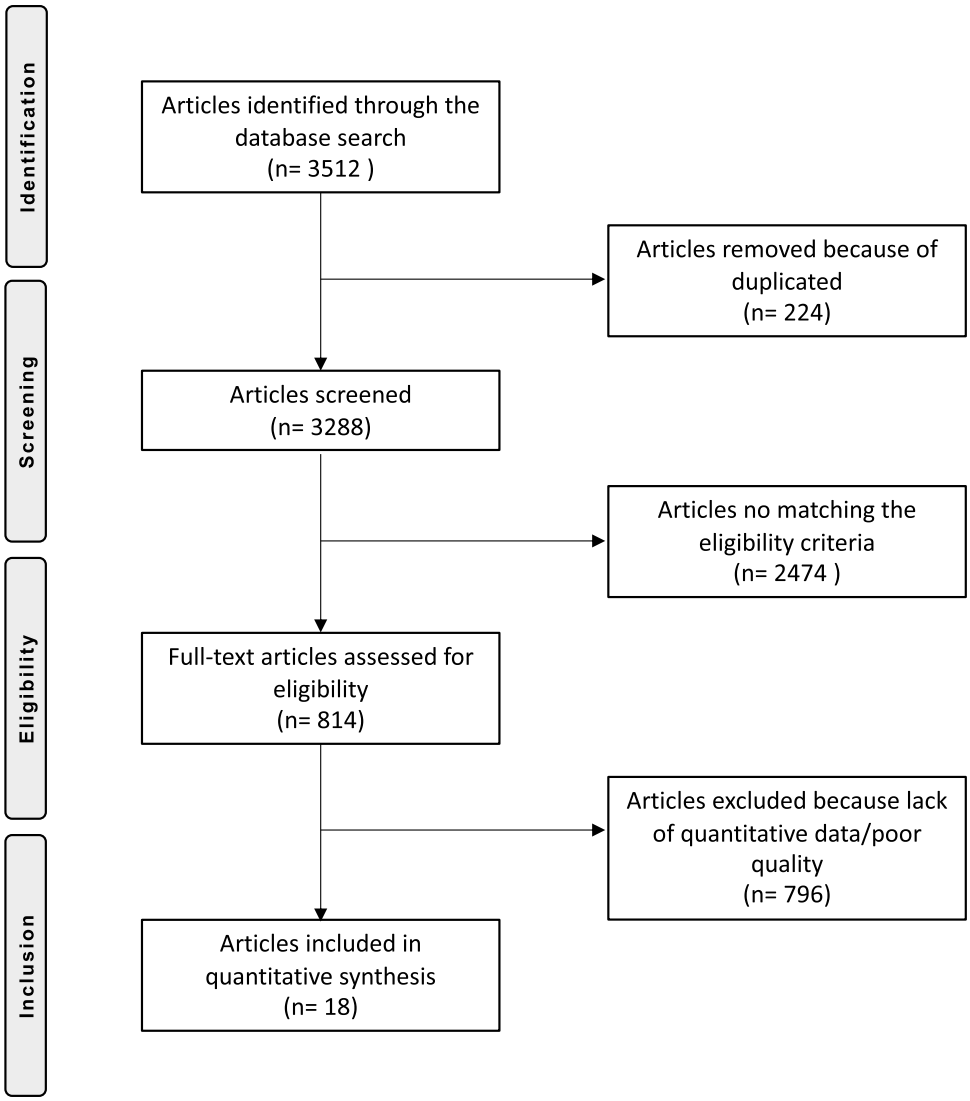

Fig. 1 PRISMA flow-chart of the literature search

Subgroup analysis

Due to lack of quantitative data, in the subgroup analysis only the VAS, WOMAC and walking distance were evaluated. Concerning donor source (adipose vs bone marrow), no statistical differences were found concerning VAS (EE 3.97; 95% CI 0.01–5.15, $P = 0.68$), WOMAC (EE 5.12; 95% CI 3.56–6.99; $P = 0.21$) and walking distance (EE 2.17; 95% CI 1.36–3.16; $P = 0.48$). Concerning the degree of degeneration, the Kellgren and Lawrence II to III evidenced statistically significant greater VAS (EE 15.79; 95% CI 11.91–16.77, $P = 0.03$), WOMAC (EE 9.94; 95% CI 5.40–11.99; $P = 0.05$) and walking distance (EE 27.51; 95% CI 18.49–33.15; $P = 0.004$).

Complications

A total of 136 (12.7%) local complications were detected. In 130 cases, pain and swelling were reported: of these, 35 were rated as mild, 2 as moderate, and 2 as intense knee pain. Other complications included one case of skin reaction, two cases of allergic reactions, and two hematomas. Complications requiring surgery during the follow-up time were: one total knee replacement and one acute meniscus lesion.

Table 1 Demographic baseline and result of the CMS of the enrolled studies

Authors, year	Type of study	Mean Coleman Score	Mean age	Mean follow-up (months)	Knees (*n*)	Control group	Cell source	Dose (10^6)	Criteria	
									Inclusion	Exclusion
Al-Najar et al. 2017 [21]	Prospective cohort study	59	50	6, 12	13	N	Bone marrow	61	(1) Age 18–65 (2) Symptoms > 6 months (3) Kellgren and Lawrence 2 to 3 (4) Absence of local or systemic infection (5) Absence of significant haematological disease (6) Absence of general blood tests abnormalities (7) Informed consent form signed by the patient	(1) Intra-articular treatment in the past 6 months (2) Significant deformity of the knee (3) Ligament or meniscus injury (MRI) (4) HBV, HCV, HIV positive (5) BMI > 30.5 (6) Pregnancy (7) Neoplasia (8) Immunosuppressive therapies
Bastos et al. 2018 [22]	Prospective cohort study	68	57.8	12	18	N	Bone marrow		(1) Age > 35 (2) Suggestive X-rays	(1) Diabetes mellitus (2) Glaucoma (3) Immunodeficiency and/or use of Immunosuppression (4) Neoplasia and/or chemotherapy (5) Infection or active wound in the knee (6) Post-traumatic OA (7) Systemic inflammation (8) BMI > 40 (9) Pregnancy (10) Other conditions that may discourage participation in the study
Centeno et al. 2014 [23]	Prospective cohort study	53	54.6	6	840	N	Bone marrow			

Table 1 (continued)

Authors, year	Type of study	Mean Coleman Score	Mean age	Mean follow-up (months)	Knees (*n*)	Control group	Cell source	Dose (10^6)	Criteria	
									Inclusion	Exclusion
Davatchi et al. 2016 [24]	Prospective cohort study	51	58.7	6, 12	4	N	Bone marrow	8.5	(1) Moderate-severe OA of both knees (2) Pain aggravated by walking or stair climbing (3) Crepitus and ROM limitation (4) Suggestive X-rays	
Emadedin et al. 2012 [25]	Prospective cohort study	58	54.56	6, 12	6	N	Bone marrow	22	(1) Ages 18–65 (2) Suggestive MRI (3) No CCs or NSAIDs (1 month prior and 6 months after procedure)	(1) Neoplasia (2) Pregnancy or lactating (3) Active neurologic and/or endocrine disorder (4) Active cardiac and/or respiratory disease requiring therapy (5) HBV, HCV, HIV positive (6) History of allergic reaction to one of the treatment components
Emadedin et al. 2015 [26]	Prospective cohort study	63	18–65	6, 12	6	N	Bone marrow	55		(1) CNS and peripheral nerves disorders (2) Any end-organ damage (3) Uncontrolled diabetes or thyroid diseases (4) Respiratory diseases (5) Pregnancy (6) History of allergic reaction to one of the treatments components
Fodor et al. 2016 [27]	Prospective cohort study		12		8	N	Adipose tissue		(1) Any CCS injection in the last 6 months (2) Any hyaluronic injection in the last 3 months	

Table 1 (continued)

Authors, year	Type of study	Mean Coleman Score	Mean age	Mean follow-up (months)	Knees (*n*)	Control group	Cell source	Dose (10^6)	Criteria	
									Inclusion	Exclusion
Garay-Mendoza et al. 2018 [28]	Prospective cohort study	60	55.67	6	26	Y	Bone marrow		(1) Age > 30 (2) Clinical suggestive of OA (3) Progression > 6 months (4) Kellgren and Lawrence 2–3	(1) Systemic arthritis (2) Knee infection or surgery in the last 6 months (3) Any intra-articular injection in the past 3 months (4) Neurodegenerative or autoimmune diseases (5) Neoplasia (6) Secondary OA
Goncars et al. 2018 [29]	Prospective cohort study	61	53.96	6, 12	34	N	Bone marrow		(1) Neoplasia (2) Presence of severe diseases (3) Contracture or instability (4) Deformity (5) secondary OA (6) Previous use of CCS or immunosuppressive (7) Previous injection within 2 months	

Table 1 (continued)

Authors, year	Type of study	Mean Coleman Score	Mean age	Mean follow-up (months)	Knees (*n*)	Control group	Cell source	Dose (10^6)	Criteria	
									Inclusion	Exclusion
Lamo-Espinosa et al. 2016 [30]	Randomized clinical trial	66	61.8	6, 12	16	Y	Bone marrow	10, 100	(1) Age 50–80 (2) diagnosis of knee OA according to American College of Rheumatology criteria (3) VAS ≥ 2.5 (4) Kellgren and Lawrence 2–4 (5) BMI 20–35 (6) Availability to the follow-up	(1) Polyarticular disease (2) Knee deformations (3) Rheumatic disease (4) Arthroscopy or intraarticular infiltration in the last 6 months (5) Chronic Immunosuppressive or anticoagulant drugs (6) CCS treatment in the 3 last months (7) NSAIDs in the last 15 days (8) Severe bilateral knee OA (9) Non-controlled diabetes mellitus (10) blood dyscrasias (11) Any allergy to HA or bird proteins
Lamo-Espinosa et al. 2018 [31]	Prospective cohort study	57	49	6, 12	12	N	Bone marrow	40	(1) Kellgren and Lawrence 2– 4 (2) Chronic knee pain of mechanical origin (3) Absence of local or general infection (4) Any hematologic and biochemical alterations (5) Patient can understand the nature of the study (6) Informed written consent provided by the patient	(1) Age 10 to 75 (2) HBC, HCV, HIV, syphilis positive (3) Congenital or acquired knee deformities (4) BMI > 30 (5) Pregnancy or breast-feeding (6) Neoplasia (7) Immunosuppression (8) Intra-articular injection in the previous 3 months (9) Other conditions that may discourage participation in the study

Table 1 (continued)

Authors, year	Type of study	Mean Coleman Score	Mean age	Mean follow-up (months)	Knees (*n*)	Control group	Cell source	Dose (10^6)	Criteria	
									Inclusion	Exclusion
Orozco et al. 2013 [32]	Randomized clinical trial	62	61.8	48	16	Y	Autologous iliac crest BM	10, 100	Ringer lactate (1) Age 50–80 (2) diagnosis of knee OA according to American College of Rheumatology criteria (3) VAS ≥ 2.5 (4) Kellgren and Lawrence ≥ (5) BMI 20–35 (6) Availability to the follow-up	(1) Polyarticular disease (2) Knee deformations (3) Rheumatic disease (4) Arthroscopy or intraarticular infiltration in the last 6 months (5) Chronic Immunosuppressive or anticoagulant drugs (6) CCS treatment in the 3 last months (7) NSAIDs in the last 15 days (8) Severe bilateral knee OA (9) Non-controlled diabetes mellitus (10) blood dyscrasias (11) Any allergy to HA or bird proteins
Pers et al. 2016 [33]	Prospective cohort study	49	64.9	6	18	Y	Adipose tissue	2, 10, 50	(1) Age 50–75 (2) Kellgren and Lawrence 3–4 (3) Symptomatic primary idiopathic knee OA at least in the last 12 months	(1) Autoimmune disorders or previous neoplasia in the past 5 years (2) Previous oral or intra-articular CCS and hyaluronic within 6 months
Pintat et al. 2017 [34]	Prospective cohort study	55	43.1	6, 12	19	N	Adipose tissue		(1) Age 20–60 (2) No X-Ray alterations (3) MR suggestive of OA	(1) Pregnancy (2) Infections (3) Previous CCS injection of the knee (4) immunodeficiency

Table 1 (continued)

Authors, year	Type of study	Mean Coleman Score	Mean age	Mean follow-up (months)	Knees (*n*)	Control group	Cell source	Dose (10^6)	Criteria	
									Inclusion	Exclusion
Rajput et al. 2018 [35]	Retrospective cohort study	45	61.2	6, 12	11	N	Bone marrow		(1) Age 40–75 (2) Radiological and clinical suggestive (3) Any liver and renal function's alterations (3) Controlled diabetes (if diabetic) (3) Informed consent signed by the patient	(1) Knee deformations (2) Any other cause of leg pain (3) Secondary OA
Soler et al. 2016 [36]	Prospective cohort study	65	52	6, 12	15	N	Bone marrow	40.9	(1) Kellgren and Lawrence 3–4 (2) Chronic mechanical knee pain (3) Absence of septic process (4) Any haematological and biochemical alteration (5) Informed Consent Form signed by the patient (6) The patient can understand the nature of the study	(1) Age 18–75 (2) Previous knee surgery (3) Intraarticular treatment in the past 6 months (4) Knee ligament or meniscus injuries (MRI) (5) Infection (6) HBV, HCV, HIV, syphilis positive (7) Knee deformations (8) BMI > 30.5 (9) Pregnancy (10) Neoplasia (11) Immunosuppression (12) Other conditions that may discourage participation in the study
Soler Rich et al. 2015 [37]	Prospective cohort study	50	57,8	12	50	N	Bone marrow	40	(1) Kellgren and Lawrence 2–4 (2) Conservative treatment for at least 6 months	
Spasovski et al. 2018 [38]	Prospective cohort study	62	63	6, 12	11	N	Adipose tissue		(1) Neoplasia (2) Endocrine disorders	

Table 1 (continued)

Authors, year	Type of study	Mean Coleman Score	Mean age	Mean follow-up (months)	Knees (*n*)	Control group	Cell source	Dose (10^6)	Criteria	
									Inclusion	Exclusion
Vega et al. 2015 [39]	Randomized controlled trial	68	57	12	13	Y	Bone marrow	40	(1) Kellgren and Lawrence 2–4 (2) Chronic mechanical knee pain (3) Absence of local or general infection (4) Any haematological and biochemical alteration (5) Informed Consent Form signed by the patient (6) The patient can understand the nature of the study	(1) Age < 18 or > 75 (2) HCV, HBV, HIV, syphilis positive (3) Knee deformities (5) BMI > 30 (6) Pregnancy (7) Neoplasia or immunosuppression (8) Intra-articular injection of any drug in the last 3 months (9) Other conditions that may discourage participation in the study

Table 2 Overall results of the comparisons

Outcome	Baseline		6 Months		12 Months		Estimated effect, IV, Random [95% confidence interval]			
	Mean	SD	Mean	SD	Mean	SD	0–6 Months	*p*	0–12 Months	*p*
VAS	55.28	18.37	25.66	15.10	20.08	91.54	30.98 [24.07 to 37.89]	< 0.0001	36.91 [30.39 to 43.43]	< 0.0001
WOMAC	25.66	15.10	34.65	24.79	24.98	14.39	25.23 [14.93 to 35.53]	< 0.0001	15.60 [10.10 to 21.10]	< 0.0001
Walking Distance	71.90	28.41	310.24	160.69	578.33	270.31	152.22 [−309.03 to 4.58]	0.06	316.72 [−696.54 to 63.10]	0.10
Lequesne Scale	33.76	19.72			20.70	19.07			12.90 [−1.35 to 27.15]	0.08
KOOS										
Overall	41.07	12.17	36.93	38.56	65.13	13.56	8.47 [15.78 to −32.72]	0.49	18.94 [27.00 to 10.88]	< 0.0001
Symptoms	51.27	15.21	81.71	13.46	69.57	14.99	10.40 [19.88 to 0.92]	0.03	14.14 [21.35 to 6.93]	0.001
Pain	49.55	14.51	85.28	5.34	69.57	14.99	21.30 [29.69 to 12.91]	< 0.0001	22.03 [29.39 to 14.67]	< 0.0001
Function	50.36	18.90	87.76	4.33	76.87	16.02	17.80 [26.31 to 9.29]	< 0.0001	21.54 [28.84 to 14.24]	< 0.0001
Recreation	27.84	17.46	74.00	8.96	57.97	21.17	23.60 [34.27 to 12.93]	< 0.0001	23.07 [32.10 to 14.04]	< 0.0001
Quality of life	32.69	23.40	63.00	17.39	54.87	17.01	14.30 [4.41 to 24.19]	0.005	14.07 [38.98 to −10.84]	0.27

Discussion

This systematic found that MSC infiltrations for knee OA can represent a feasible option, leading to an overall remarkable improvement of all clinical and functional considered outcomes with a very low complication rate during the follow-up duration. Any statistically significant difference among adipose- and bone marrow-derived MSCs were found. Patients treated at earlier-degeneration stages reported statistically significant greater VAS, WOMAC and walking distance. The pain and function scores were improved considerably, thus, leading to a significant improvement of patient participation in recreational activities and quality of life.

Several options for knee infiltration have been suggested as conservative treatment for OA. Corticosteroids (CCS) infiltrations have been used as palliative treatment for advanced OA for many years [40]. The CCS inhibit the inflammatory cascade, causing a temporary relief from OA symptoms [41]. However, destructive effects on the articular cartilage have been extensively documented [42–45]. On the contrary, the MSCs encourage the differentiation and proliferation, negatively modulating the inflammatory cascade promoting the articular healing [46–49]. Moreover, CCS are not recommended in concomitance with MSCs infiltrations. The CCS can dose-dependently reverse the therapeutic effect of MSCs [50]. This is supported by in vitro and in vivo observations [51, 52]. However, the correlation between CCS and MSCs is still not completely clarified and requires further studies [53]. In addition, the authors excluded patients who previously underwent local anaesthetic injections since they have a cytotoxic effect on MSCs [54, 55]. Platelet rich plasma (PRP) have been extensively used in the orthopaedic and trauma surgery. Platelets are committed leucocytes derived from the fragmentation of the precursor megakaryocytes [56]. They represent a source of growth factors, promoting tissue healing and regenerative processes [57–59]. However, results concerning PRP are contrasting and no consensus has been reached [60–62]. Platelet are extracted, concentrated and re-implanted in the same day, requiring minimal cell manipulation: same characteristics for the bone marrow aspirate (BMA) [23]. The BMA is a niche of cells with multiple degree of differentiation and lineage commitment. However, the quality and quantity of cells present within the aspiration are not adequate. The estimated amount of MSCs in BMA is between the 0.01% and 0.001% [63, 64]. On the opposite, MSCs injection shows several methods of processing, culture preparation/expansion and delivery, and the various adjuvants and diluents involved. MSCs being not committed, have high proliferation and differentiation potential, can modulate the immune answer and tissue trophism [65–67].

The authors of said studies referred to different stages of the Kellgren and Lawrence Scale in their criteria [68]. Some patients were treated at early stages of osteoarthritic knee degeneration. The MSCs could potentially reverse these stages of degeneration, differentiating into every cell derived from the mesoderm germ layer including chondroblasts, adipocytes, and osteocytes [69]. The process of allocating stem cells is called "homing" and is followed by differentiation and proliferation, regenerating the damaged tissue, and healing the intraarticular cascade [46]. These processes are characterized by a wide production of growth factors, cytokines, and chemokines, giving life to a signalling pattern between the environment and the MSCs [47, 70]. In the early stages of the Kellgren and Lawrence Scale, a minimally viable substrate can still be recognized: the required condition to generate the signalling pattern. In animal models, MSCs have been successfully transplanted, reporting considerable clinical improvement and better outcomes compared to controls [71–74]. In accordance with the Kellgren and Lawrence Scale [68], other authors injected their patients at advanced or end-stage degeneration. If the environment is irreparably damaged, however, how can stem cells interact with them? What is the role of stem cell infiltration? In addition to their homing ability, stem cells showed intrinsic immunomodulation ability [75]. Stem cells interact with the NK cells, macrophages and lymphocytes, inhibiting the proliferation, chemiotaxis, and promoting cytotoxic action of immune cells [46, 48, 49, 76, 77]. With the OA also being characterized by the activation of inflammatory and catabolic cascades [78, 79], it becomes apparent that patients suffering from knee OA can still experience relief and improvement of the aforementioned scores.

This study has several limitations; therefore, data must be interpreted with caution. The most important limitation of the present study are the heterogeneous methods of processing, culture preparation/expansion and delivery, and the various adjuvants and diluents involved. This underlines how our competences are not yet sufficient to understand which is the most effective methods of dealing with MSCs. Furthermore, the different legislations of certain countries that limit or prohibit the use of MSCs in humans, having a negative impact on the overall development and knowledges of MSCs. Other considerable limitations were the heterogeneous inclusion and exclusion criteria and lack of appropriate controls, representing remarkable sources of selection bias, purposely done to increase the pooling data. Further significant limitations exist due to the low level of evidence of the included studies and the limited follow-up duration. Based on a lack of existing data, it was not possible to analyse other follow-up terms. Points of strength of this study are the comprehensive nature of the research, along with the strict eligibility criteria. We excluded several works to ensure the best evidence possible concerning these increasingly

expanding therapies. In the literature there are contrasting evidences and a lack of consensus regarding the best cell source (bone marrow, adipose, peripheral blood) and further studies should be addressed to clarify this point. Due to lack of evidences and data in the literature, we only focused in adipose- and bone marrow-derived stem cells. This represent a limitation of this study. Further study should also provide randomization and blinding methods, along with a longer follow-up and group control.

Conclusion

According to the current evidences and the main findings of this systematic review, we reported that MSC infiltrations for knee OA can represent a feasible option, leading to an overall remarkable improvement of all clinical and functional considered outcomes with a very low complication rate during the follow-up duration. No difference among adipose- and bone marrow-derived MSCs were found. Patients treated at earlier-degeneration stages reported statistically significant greater outcomes. The pain and function scores were improved considerably, thus, leading to a significant improvement of patient participation in recreational activities and quality of life.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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