Review

Regenerative Medicine

Current evidence on mesenchymal stem cells for hip osteoarthritis: a narrative review

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There are limited data on the use of mesenchymal stem cell injections for hip osteoarthritis. The goal of this study was to evaluate the literature by analyzing outcomes and comparing methodologies. Online search of PubMed, SportsDiscus and Case Reports Keywords was completed using the keywords 'stem cells' and 'hip' and 'osteoarthritis'. Six studies met the inclusion and exclusion criteria. Five out the six studies had statistically significant improvement in patient reported outcomes after mesenchymal stem cell injections. Only two studies provided information on radiological changes and findings were positive. None of the studies reported major complications. Small series of non-randomized controlled trials completed to date in the use of mesenchymal stem cells for the treatment of hip osteoarthritis reported the procedures to be safe and provide a positive clinical response. Randomized controlled trials must be performed to further confirm mesenchymal stem cells as a treatment option for hip osteoarthritis.

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Osteoarthritis (OA) is a degenerative joint disease that causes destruction of the chondrocytes through destructive inflammatory cytokines, metalloproteinases and mechanical stress which subsequently leads to joint space narrowing, formation of osteophytes and subchondral cysts [1]. The median age of diagnosis of OA is 55 [2]. Globally about 240 million adults, 32 million of which are in the United States, suffer from symptomatic OA and the prevalence is expected to continue to rise due to the increase in life expectancy [3,4]. When symptomatic, OA can lead to pain, stiffness, and loss of range of motion. Factors that contribute to the development of OA include genetics, gender, mechanical stress, and prior trauma. It predominantly affects weight bearing joints, most commonly the knee followed by the hip [5,6]. Diagnosis is made clinically and radiological images are not required for the diagnosis [7]. Nonetheless, two x-ray based scales are generally utilized to classify the severity of OA of the hip. The Tönnis classification of hip OA is a grading scale specific to hips which grades the severity of hip OA on a scale of 0–3, with 0 being no signs of hip OA to 3 being severe hip OA [8]. The Kellgren-Lawrence scale utilizes a 0–4 grading in which 0 is no arthritis, 1 is doubtful, 2 minimal, 3 moderate and 4 severe [9].

Current treatments of OA include nonoperative and operative management. Initial nonoperative treatments include weight loss and physical therapy with the goal of improving biomechanics [10,11]. This can result in a reduction of mechanical stress placed on the cartilage which can help slow down the progression of OA, increase range of motion, decrease pain and improve function [12]. Pharmacologic intervention like topical and oral anti-inflammatories can be used to manage symptoms of OA however the latter comes at risk of more side effects [13]. Recent guidelines (NICE) do prefer topical treatments over oral [7,14].

When physical therapy and anti-inflammatories fail to manage symptoms of OA, injections of steroids and hyaluronic acid (HA) into the affected joint can be used [15,16]. Steroid injections can decrease the inflammatory environment within the arthritic joint. However, steroid injections provide temporary relief and repeated doses can lead to further destruction of the joint [17,18]. HA injections work to decrease intra-articular inflammation and enhance joint mobility [19]. Currently in the USA, HA these is only FDA approved for knee OA [20] Studies completed with hyaluronic acid injections for hip OA led to short-term relief [21]. However, when compared with other forms of injections it did not appear to provide superior response [22–24]. In light of the limited treatment options, joint arthroplasty is sought out as a definitive treatment option. However, joint arthroplasty carries its own risks: substantially more invasive, infection, persistent pain, leg length discrepancy, and elevated costs. It also

Future Medicine

requires long post-operative rehabilitation, and may require revision if the surgery fails, or if the components wear out over time [25]. Additionally, there are a subset of patients who suffer from OA and may not qualify for surgery or due to young age joint arthroplasty is not recommended. Due to these multiple reasons, there is a gap on the non-invasive interventions for OA.

With debilitating symptoms, chronicity of the disease and no disease modifying drug, OA can be challenging to treat. To assist patients in the OA treatment gap, physicians have been utilizing orthobiologics, which includes platelet-rich plasma (PRP) and cellular therapies such as bone marrow aspirate concentrate (BMAC) and mesenchymal stem cells derived from fat to treat pain and improve function. All three of these intra-articular therapies were well tolerated with no significant short term and long term adverse reactions reported and no significant difference between them as well [26–29]. PRP aims to enhance tissue repair by providing a pro-inflammatory response through the injection of concentrated cytokines, proteins, and growth factors [30]. Randomized controlled trials and systematic reviews with PRP for knee OA have demonstrated to provide pain relief ranging from 6 to 12 months [26,31,32]. Nonetheless, other studies reported no significant difference [33,34]. A key observation is the substantially lower platelet concentration in some studies [34]. For hip OA, meta-analyses of PRP have not demonstrated a significant difference from HA and the effects when present were noticeable only for 2 months [22]. It is important to note, that there is variation between studies between number of injections, severity of the disease, and platelet concentration which can negatively impact the interpretation of the results [35]. The higher the OA grading, the less response to any injectables [36,37]. In particular to PRP, the dose of 1 million platelets indicates superiority in bone growth and probably should be a target for OA [38].

For this reason, cellular therapy has been researched due to its multifaceted characteristics and higher likelihood of joint enhancement in comparison to PRP characteristics. It combines cytokines and mesenchymal stem cells (MSCs), when PRP has cytokines alone. MSCs possess multiple immunomodulatory and anti-inflammatory mechanisms of action. These have been outlined as suppression of $CD4^+$ and $CD8^+$ lymphocytes, expression of Toll-like receptor (TLR)-2 and -8 receptors, and inhibition of the action of the dendritic cells [39]. All these different actions lead to cytokine and immune response modulation leading to increase production of IL-10, decrease of TNF-α and IFN-γ [39]. Furthermore, macrophage modulation by MSCs plays an important role in OA progression. After MSC injections there is a transformation of M1 to M2 macrophages. M2 macrophages are known as wound-healing macrophages by producing IL-10, IL-1RA, chemokine ligand 18 and TGF-b [40]. Another positive aspect is that BMAC appears to provide a consistent response despite age [41].

There is interest in the role of adipose derived MSCs (ADMSC) in tissue regeneration. ADMSC contain more cells than BMAC, possess anti-inflammatory properties, and are less invasive to acquire [42,43]. Due to a higher volume of acquisition, a greater number of joints could be treated. Other argue that BMAC would be superior due to unique characteristics such as the osteochondroreticular (OCR) stem cells in the bone marrow [44]. However, no superiority of either intervention has been identified [45]. However, until now it has not been proven that MSC's can regenerate tissue *in vivo* [46,47].

Currently MSC injections are being used for the treatment of both knee and hip OA. Despite multiple studies, the quality of the studies is mixed. This makes interpretation of MSC therapy for the treatment of OA complex [48,49]. For knee OA, there are several RCTs and cohorts have been completed allowing the summation of the data in a systematic review. Due to the paucity of data of MSCs studies for hip OA, the purpose of this first narrative review was to analyze current data available for responsiveness and safety.

Methods

A review was completed in January 2022 of the existing literature regarding the utilization and efficacy of MSC for the treatment of hip OA. The search used the electronic database PubMed, SportDiscus and Case Reports from 1998 to 203. Keywords used in the search were 'stem cells' and 'hip' and 'osteoarthritis'. Inclusion criteria included articles which described human clinical studies written in English. Articles were excluded if they addressed inflammatory arthropathies, avascular necrosis or focal chondral defects. Articles that assessed combined interventions (i.e., PRP and MSCs). Review papers and studies evaluating the use of MSC in other joints that were not the hip were excluded. Animal, basic science and epidemiology studies were excluded as well as editorials and surgical technique papers. A total of 138 articles were identified on the initial search of articles and abstracts according to the screening criteria but, only six of the 138 articles satisfied all criteria for review acceptance (Figure 1). Data were then analyzed from the six articles. The main outcome variables of interest were number of participants, radiological grading scale of the hips studied, injection type, number of injections, follow-up duration, patient

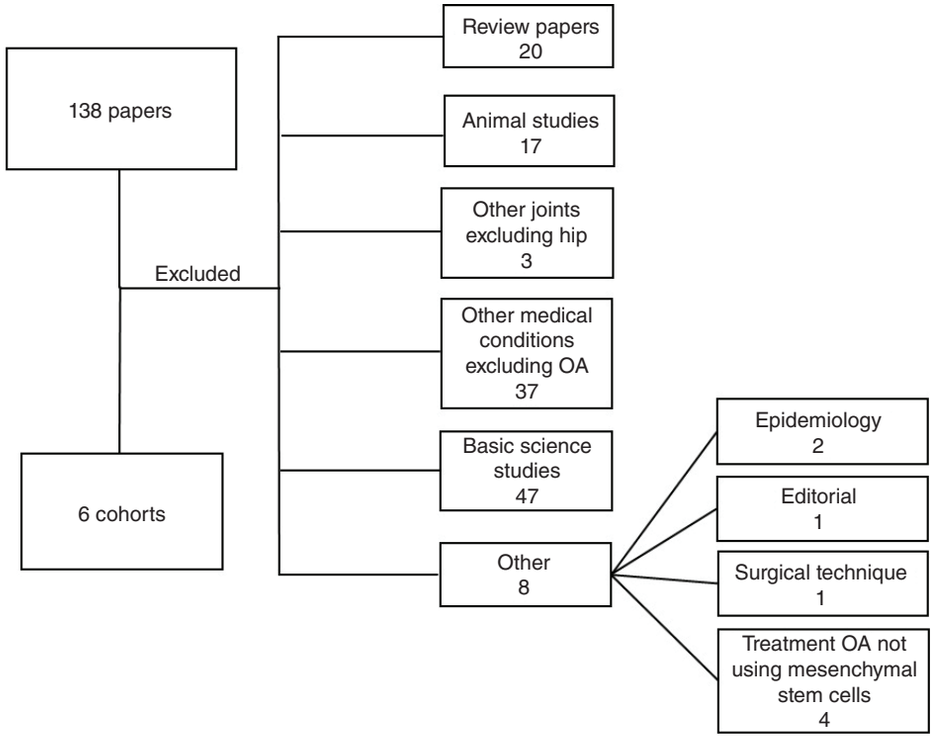

Figure 1. Flow diagram outlining literature review.

reported outcome scores, and adverse reactions. Delta VAS and minimal important clinical difference (MCID) was assessed when information was provided.

Results

Six studies reported the clinical outcomes of MSC therapy for the treatment of hip OA with a total of 61 hip joints. Due to the small number of joints, a systematic review was not able to be completed. The average follow-up time across the studies was 14.1 months, with a range of 1.8 months to a maximum follow-up time of 34.8 months. Some studies had short term assessments at 6 weeks and 3 months [50]. For the purpose of the data comparison, the longest follow-up was utilized by each study.

There was wide variance between the studies in light of different patient reported outcomes, follow-up time and reporting of the results across all studies. None of the studies had any form of control group. Five out of six the studies achieved statistically significant improvement in at least one patient reported outcome score [50–54]. Patient reported outcome scores varied among studies and are listed by each study on Table 1. Most of the hip joints studied utilized autologous BMAC injections in which three studies (Figure 2) resulted in statistically significant improvement in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores after injection with MSC [51,54]. Modified Hip Harris Score (mHHS) is the Hip Harris Score (HHS) without the physician assessment. Both scores were also utilized for the study. All the studies that evaluated VAS [52–54] and HHS [50,52–54] (Figure 3) observed statistically significant improvement after MSC injection from initial baseline measures. Five out of six studies achieved MCID for at least one of the reported PROMs [50–54] The MCID threshold for WOMAC was a difference of at least 9.1 and was achieved by five of the studies [50–55]. The MCID threshold for mHHS and HSS was a difference of at least 17 and was achieved by only four of the studies [50,52–54].

Radiographic imaging was assessed with x-ray imaging and magnetic resonance imaging (MRI) and were utilized as surrogates to evaluate cartilage regeneration. In the study by Madrones *et al.*, x-ray images acquired more than 2 years after injection demonstrated maintenance of Tönnis scale grade from baseline [52]. The study done by Emadedin *et al.* reported MRI evidence of increased cartilage thickness in 60% (n = 3) of the patients, however the magnitude of improvement was not described [53].

Table 1. Analysis of study characteristics.

Study	Design	n	Tönnis scale	Type of injection	Number of injections	Mean final follow-up (months)	PROMs	Delta VAS	MCID achieved?	Ref.
Mardones	Case series	13	1-3	Autologous expanded BMAC	3 (1 wk apart)	27.4 ± 7.4	VAS (SSI) WOMAC (NSI) mHSS (SSI) VAIL (SSI)	3.1 (SSI)	Yes: mHSS, WOMAC	[52]
Emadedin	Cohort	5	2-3	Autologous expanded BMAC	1	30	VAS (SSI) WOMAC (NR) HSS (SSI)	N/A	Yes: WOMAC HSS	[53]
Darrow	Case series	4	1-3	Autologous BMAC	4	3.4 ± 1.6	LEFS (NR)	N/A	NR	[65]
Rodriguez-Fontan	Cohort	15	1-2	Autologous BMAC	1	13.2 ± 6.3	WOMAC (SSI)	N/A	Yes: WOMAC	[51]
Whitney	Case series	18	2-3	Autologous BMAC	1	6	WOMAC (SSI) mHHS (SSI) SF-12 PCS (NSI) SF-12 MCS (NSI) NRS pain at rest (SSI) NRS pain with activity (SSI) HOS-ADL (SSI)	N/A	Yes:WOMAC, mHHS	[50]
Dall'Oca	Retrospective review	6	0-2	Autologous adipose-derived mesenchymal stem cells	1	6	VAS (SSI) WOMAC (SSI) HHS (SSI)	N/A	Yes: WOMAC, HHS	[54]

BMAC: Bone marrow aspirate concentrate; HSS: Harris hip score; HOS-ADL: Hip outcome score-activities of daily living; LEFS: Lower extremity functional scale; MCID: Minimal clinical important difference; mHSS: Modified Harris hip score; N: Sample size; N/A: Not applicable; NR: No statistical test reported; NRS: Numeric rating score; NSI: Non-statistically significant improvement; RR: Retrospective review; SSI: Statistically significant improvement; SF-12 PCS: 12-Item short form health survey physical component summary; SF-12 MCS: 12-Item short form health survey mental component summary; VAIL: Vail hip score; VAS: Visual analog scale; WOMAC: Western Ontario and McMaster Universities osteoarthritis index.

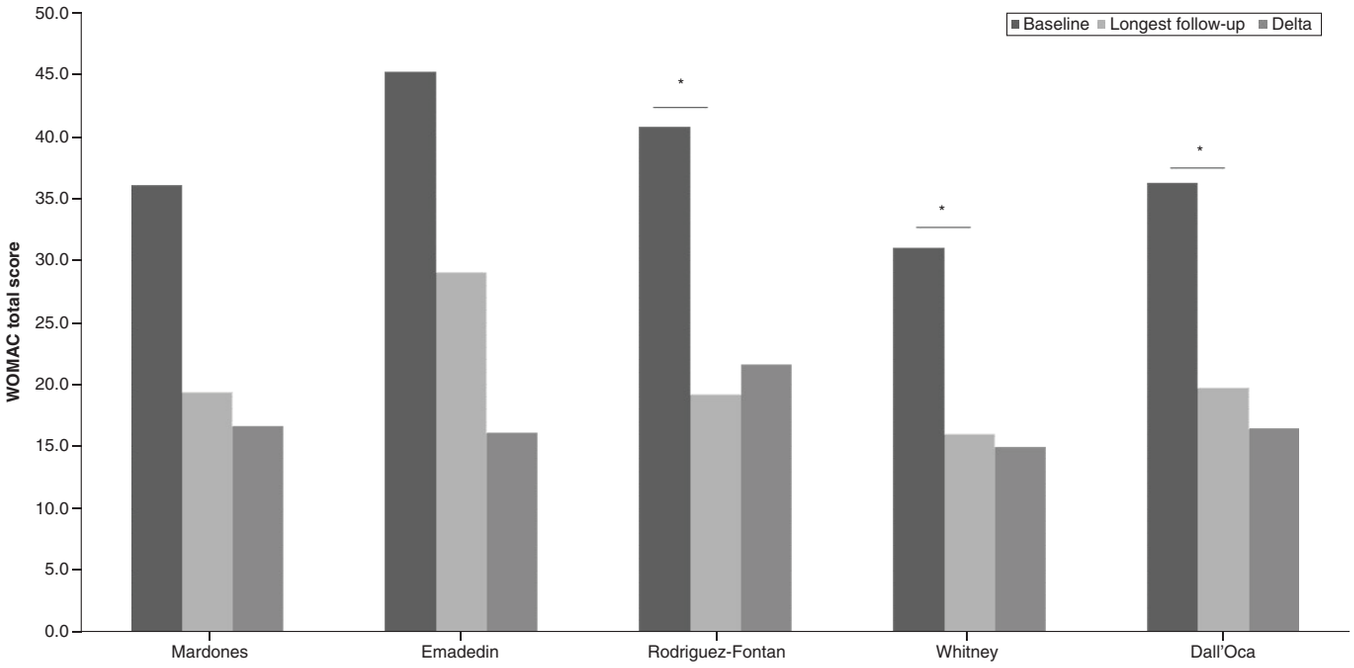

Figure 2. Western Ontario and McMaster Universities osteoarthritis index comparison baseline to follow-up.
*Statistically significant difference between baseline and follow-up.
Delta – Difference in score between baseline and follow-up.

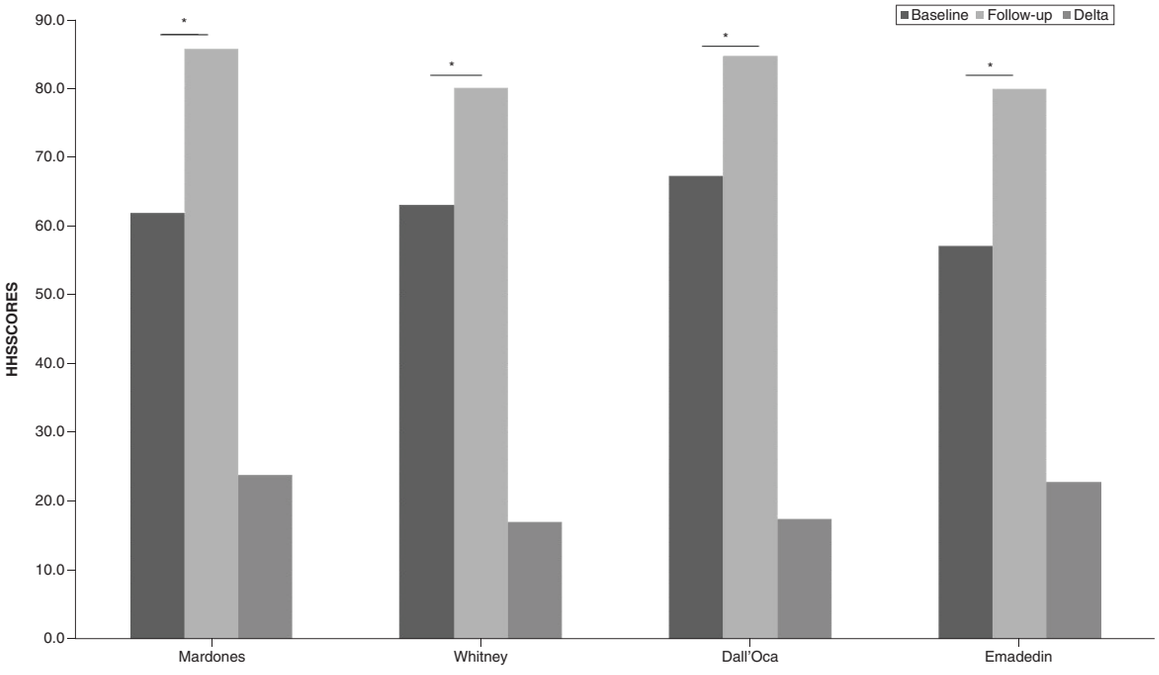

Figure 3. Hip Harris Score comparison baseline to follow-up.
*Statistically significant difference between baseline and follow-up.
Delta – Difference in score between baseline and follow-up.

Adverse reactions

No significant adverse effects or major complications were reported across all the studies. The complications that occurred were limited to the injection site that included short term erythema, hematoma, edema and pain [51,53,54].

Infectivity

Emadedin *et al.* tested the bone marrow aspirate and completed culture growth that was negative for pathogens [53]. Emadedin *et al.* also assessed long term safety with subsequent blood work up to 30 months following injections [53]. Emadedin results were unchanged from baseline.

Discussion

The emergence of mesenchymal stem cells for treatment of osteoarthritis

The lack of effective treatment of OA is a substantial challenge to healthcare as the population ages and healthcare expenditure increases [56]. MSCs have become an attractive treatment modality for OA because they are safe, minimally invasive and have regenerative, anabolic, anti-inflammatory potential. Stem cells for the treatment of knee OA has been more widely studied than treatment of hip OA through several randomized controlled trials that have provided more evidence of its clinical response [57,58]. Nonetheless, careful attention is necessary to the clinical outcomes selected by the studies as the literature is analyzed. In a study done by Shapiro *et al.*, 25 patients with bilateral knee OA received a BMAC injection in one knee and a saline placebo into the other knee, which resulted in significant decrease in overall knee pain at 12-months follow-up with no difference between BMAC and saline injected knees. There was also a lack of significant in changes in T2 quantitative MRI mapping of both the BMAC and saline placebo-injected knees [58]. Even though studies have demonstrated improvement in patient reported outcomes after the use of MSC for treatment of knee OA [59,60], it cannot be assumed these results can be reciprocated in a hip joint with OA due to differences in joint composition and mechanics [61]. Our review of the literature demonstrated that small studies with different types of MSC are safe and provide pain relief on average for 6 months and potentially more. There was variation on follow-up time within the studies assessed. Nonetheless, level 1 data by a randomized control trial for hip OA has not yet been published. This can be due to the knee being the most common joint affected by OA in addition to the complex regulatory environment for the completion of an investigational device exemption (IDE) or investigational new drug (IND) applications with the US FDA and costs related to the completion of a randomized control trial.

Study strengths

The six studies included used different types of MSC injections to the hip joint. Despite different methodologies, no significant adverse reactions were reported. The changes in the patient reported outcomes have been sufficient on occasion to reach MCID, indicating a clinical and statistical improvement. Out of the six studies, five provided minimum data to assess MCID. As further research is completed with MSCs it important to ensure that both clinical and statistical changes are achieved.

Study limitations

Several limitations of this review can impact the conclusions. These are the small sample size, use of different patient reported outcomes, different types of MSC injections and MCID being calculated by means (raw data per patient only available in one study).

There was a broad range of follow-up time across the six studies spanning from 1.8 to 34.8 months. The variability of follow-up time between the studies interferes with the interpretation of the duration of the response especially considering the lack of data available. For this reason, the longest follow-up was utilized in the main comparison.

The main patient-reported outcomes score selected were WOMAC, HHS and mHHS. The WOMAC has pain, stiffness and functional activities which include activities of daily living (ADL) including rest and sleeping. The HHS has only eight patient questions (one for pain, three for function related to gait and four related to activities). It also possesses additional inquiries related to deformity and range of motion which are completed by the physician [55,62,63]. The mHHS consists only the patient reported questions [64]. Despite being similar, the HHS and mHHS are focused on predominantly on activity which could have different responses to interventions.

Furthermore, it remains unclear what preparation of bone marrow versus expanded bone marrow versus adipose-derived stem cells provides superior clinical outcomes. Also, there was lack of standardization of the number of cells

that should be contained within each injection. The paper by Madrones *et al.* was the only paper that reported cell characterization information with each injection, an average of 60×10^6 cells [52]. The number of injections and time frame between multiple injections also varied. Two of the studies utilized more than one type of injection [52,65]. In the study done by Darrow *et al.* four consecutive injections were given 14 days apart due to the hypothesis that there is growth factor secretion from cells that participate in wound healing during this time [65]. However, the studies that utilized more than one injection in comparison to only one injection both resulted in statistically significant patient reported outcomes.

There was variability between patient demographics and Tönnis grade of hip OA between studies. Two of the studies focused on hips of a higher a Tönnis scale (2-3 Tönnis scale) [50,53]. This is important because it can be hypothesized that hips with a higher Tönnis grade, have worse disease and therefore lower clinical response to BMAC injections. MCID might vary according to the patient population and reference, which impacts the analyses [49].

Conclusion

The use of stem cells for hip OA appears to be safe and shows promising clinical outcomes in small case series. However, large-scale randomized controlled trials need to be performed to conclude the clinical efficacy, and further standardization in reporting the MSC makeup is important for further advancement of the field.

Future perspective

OA has a high disease burden that will continue to increase due to an increase in life expectancy [4]. A delay or reversal of the current OA prevalence is important to decrease disease burden on patients and decrease healthcare costs related to joint arthroplasty. The goal is to allow patients to maintain functionality and decrease pain. As the field evolves standardized reporting of the number of MSC injected is important to determine the best clinical outcomes. Furthermore, patient optimization will be essential prior to injections of MSCs, which will lead to the potential increase in MSCs. A randomized control trial for MSC use for the treatment of hip OA is lacking. Nonetheless, this review with small clinical studies on the use of MSCs for the treatment of hip OA has demonstrated safety and significant clinical effectiveness, indicating the necessity for further research [30–34,43].

Summary points

- Osteoarthritis (OA) is a degenerative joint disease that causes destruction of the characterized by joint space narrowing, formation of osteophytes and subchondral cysts.
- When symptomatic, OA can lead to pain, stiffness and loss of range of motion.
- Globally about 240 million adults suffer from symptomatic OA and the prevalence is expected to continue to rise due to the increase in life expectancy.
- Current available nonoperative treatment modalities of hip OA are physical therapy, weight loss, activity modification, topical and oral anti-inflammatories as well as intra-articular steroid, hyaluronic acid, platelet-rich plasma and mesenchymal stem cells (MSCs) injections.
- Current definitive treatment of hip OA is joint arthroplasty.

Methodology

- This is the first review paper evaluating the current evidence of MSCs use for the treatment of hip OA.

Results

- Six small studies met inclusion and exclusion criteria of this review that evaluated the use of MSCs for the treatment of hip OA, which demonstrated clinical safety and clinically significant improvement of patient-reported outcomes.
- A randomized control trial study evaluating the clinical outcomes of MSCs use for the treatment of hip OA has not been completed.

Conclusion

- Larger scale randomized control trials must be completed to conclude that MSCs are effective for the treatment of hip OA.

Financial & competing interests disclosure

LP Oliveira is a consultant for Lipogems. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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