Review Article

Stem Cell INVESTIGATION

Accentuating the sources of mesenchymal stem cells as cellular therapy for osteoarthritis knees—a panoramic review

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Abstract: The large economic burden on the global health care systems is due to the increasing number of symptomatic osteoarthritis (OA) knee patients whereby accounting for greater morbidity and impaired functional quality of life. The recent developments and impulses in molecular and regenerative medicine have paved the way for inducing the biological active cells such as stem cells, bioactive materials, and growth factors towards the healing and tissue regenerative process. Mesenchymal stem cells (MSCs) act as a minimally invasive procedure that bridges the gap between pharmacological treatment and surgical treatment for OA. MSCs are the ideal cell-based therapy for treating disorders under a minimally invasive environment in conjunction with cartilage regeneration. Due to the worldwide recognized animal model for such cell-based therapies, global researchers have started using the various sources of MSCs towards cartilage regeneration. However, there is a lacuna in literature on the comparative efficacy and safety of various sources of MSCs in OA of the knee. Hence, the identification of a potential source for therapeutic use in this clinical scenario remains unclear. In this article, we compared the therapeutic effects of various sources of MSCs in terms of efficacy, safety, differentiation potential, durability, accessibility, allogenic preparation and culture expandability to decide the optimal source of MSCs for OA knee

Keywords: Osteoarthritis (OA); mesenchymal stem cells (MSCs); bone marrow; stromal vascular fraction; orthobiologics

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Introduction

The large economic burden on the global health care systems is due to the increasing number of symptomatic osteoarthritis (OA) knee patients whereby accounting for greater morbidity and impaired functional quality of life (1). The hyaline cartilage provides friction-free joint movements that protect the underlying bone from excessive load and trauma by distributing the forces equally across the joint (2). Due to the limited intrinsic healing potentiality and avascular nature of cartilage, once it gets injured, it gradually degenerates and results in OA (3). The booming ideology of "Orthobiologics" has brought up the practice of procedures that are less invasive in nature by administering substances with osteoinductive and osteogenic facets; thereby offering the benefit of decreased morbidity over classic techniques (4).

The recent developments and impulses in molecular and regenerative medicine have paved the way for inducing the biological active cells such as stem cells, bioactive materials, and growth factors towards the healing and tissue regenerative process (5). In this connotation, Mesenchymal stem cells (MSCs) are the ideal cell-based resort for treating disorders under a minimally invasive environment in conjunction with tissue regeneration (6). The efficacy of such cell therapies in animal models has been widely recognized (7,8).

MSCs act as a minimally invasive procedure that bridges the gap between pharmacological treatment and surgical treatment for OA. It provides a strong and positive balance between pro-apoptotic and anti-apoptotic molecules, pro-inflammatory and anti-inflammatory cytokines & pro-angiogenic and anti-angiogenic factors for rejuvenation of degenerated cartilaginous tissues (9). MSCs upregulate tissue inhibitors of metalloproteinases such as TIMPs-1, -3, and -4 by downregulating the signaling molecules of matrix metalloproteinases such as MMP-1, -3, -13, and -28 and upregulating ADAMTS-4 and 5 which lead to normal joint homeostasis (10).

Physiology of MSC action in OA Knee

Growth factors and BMP 2 and 7 are reported to exercise anabolic and anti-inflammatory effects and noteworthy these are present in higher concentrations in BMAC (11). There is induced production of interleukin-1 receptor antagonist (IL-1Ra) molecule in significant concentration by the MSCs and these produced molecules execute the bioactivity of inhibiting IL-1 catabolism (12). This interesting biological approach renders symptomatic relief in pain (13,14). MSCs also support neoangiogenesis through VEGF-A, VEGF-D, HGF, IGF-1, PDGF, PIGF, IL-6, EPO, MCP-1 and cellular proliferation through KGF, FGF-2, VEGF, IGF, PDGF, HGF (11,14). MSCs exerted enhanced chondroprotection through diminished pro-inflammatory mediator production and increased anti-inflammatory cytokine production including IDO, PGE2, TGF-β, TSG-6, HGF, NO, HO-1, HLA-G. They mediate their anti-apoptotic actions through VEGF, HGF, IGF-1, TGF-β, GM-CSF (12-14). A schematic diagram elaborating on the physiological action of MSC in immunomodulation of OA pathogenesis is given in *Figure 1*.

Sources of MSCs

MSCs are pluripotent cells with the potential to differentiate into the chondrogenic and osteogenic lineage. They can be derived and isolated from various autologous sources such as bone marrow, adipose tissue, synovium, endometrium, peripheral blood (PB), and allogenic sources such as placenta, umbilical cord, amniotic fluid as shown in *Figure 2*. However, evidence to delineate the ideal source of MSCs for use in OA knee remains unclear (15). In this review, we elaborate on the various types of MSCs available for therapeutic use and their merits and demerits to address the gap in knowledge in literature.

Embryonic stem cells (ESCs)

ESCs are derived from the inner cell mass of the blastocyst. Preclinical and clinical studies have proved the significant potential for cartilage engineering. ESCs are totipotent cells (16). ESCs provide numerous numbers of undifferentiated cells which may differentiate into a cell of a particular lineage (17). The cultured ESCs provide 3D scaffolds for cartilage engineering (18). ESCs are pluripotent, but their use raises ethical concerns, and additionally upon transplantation, they potentially give rise to tumors (19,20). Under the controlled growth conditions, ESCs maintained phenotype and genotype along with maintenance of MSC cell surface markers and exponential proliferation of cellular lineage (21). Toh *et al*. demonstrated neochondrogenesis and ECM production under appropriate growth factors, cytokines, and hyaluronic acid-based hydrogels (22).

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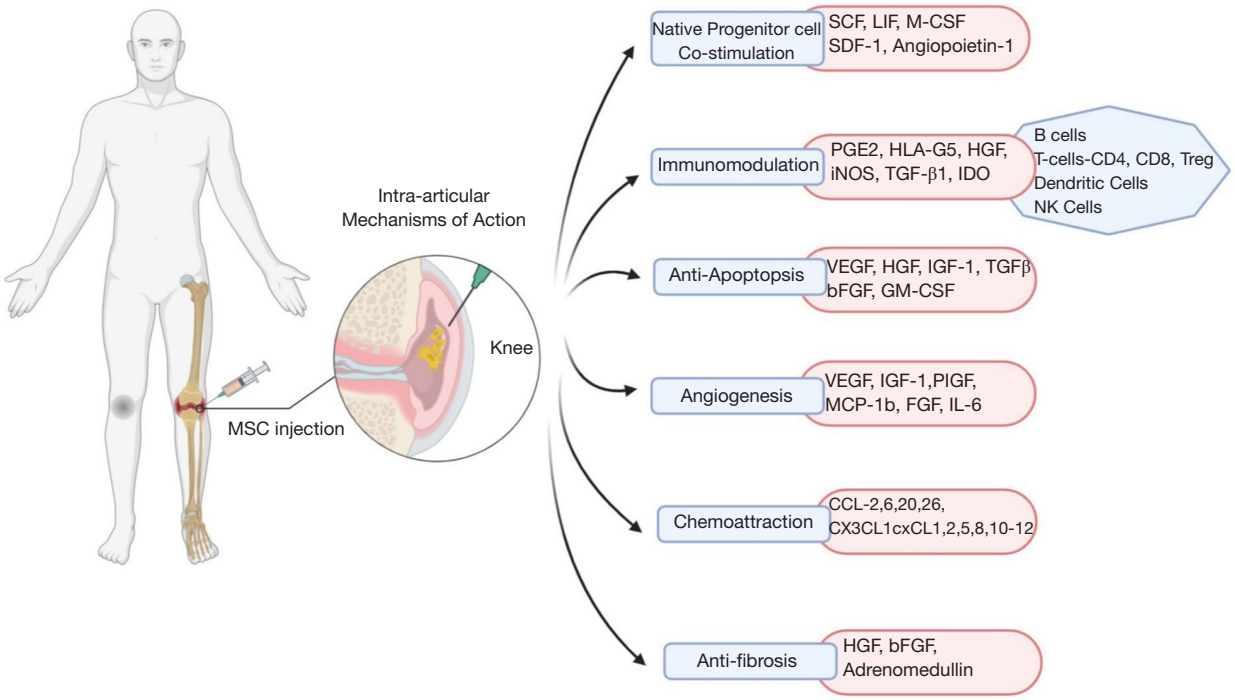

Figure 1 Schematic diagram elaborating on the physiological action of MSC in immunomodulation of OA pathogenesis. MSC, mesenchymal stem cell; OA, osteoarthritis.

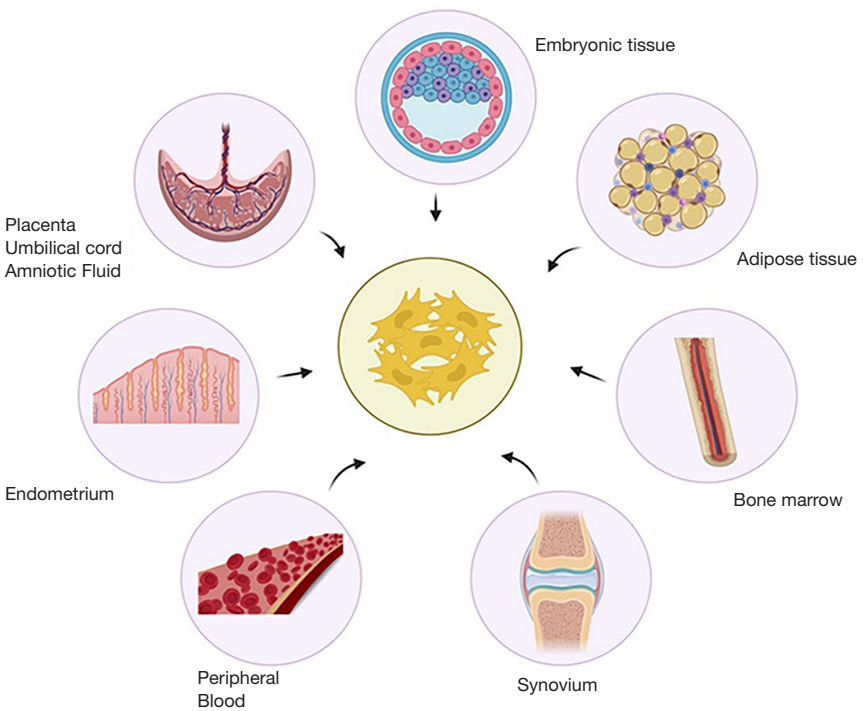

Figure 2 Sources of mesenchymal stem cells with therapeutic potential.

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Bone marrow derived MSCs (BM-MSCs)

In 1970, Alexander Friedenstein demonstrated the definitive regenerating capacity of bone marrow (23). The major source of bone marrow-derived MSCs is the iliac crest and shafts of long bones. Various researchers have reported that BM-MSCs showed fibroblastoid cells with plastic adhered morphology and non-phagocytic in nature (24,25). BM-MSCs showed differentiation towards osteogenic, adipogenic, and chondrogenic responses with the expression of endothelial or hematopoietic specific markers (26). BM-MSCs express CD146 in humans (27) and CXCL12, Nestin, leptin receptor, and Prx-1 in mice (28,29). The osteogenic potential of BM-MSC varies as a few studies prove the greater osteogenic potential (30-32) and a few prove the equal osteogenic potential (33-35) when compared with AD-MSCs. BM-MSC exhibits an inferior chondrogenic potential when compared with AD-MSC (36) and superior response when compared with Sy-MSCs (37).

Adipose tissue derived MSCs (AD-MSCs)

In recent years, the cells with major regenerative, rejuvenative, and reconstructive potentials were attributed to adipose tissue-derived MSCs due to the possession of characteristics of mesenchymal stem/stromal cells (38). AD-MSCs are isolated from lipoaspiration as an aqueous fraction from abdominal fat. The components of SVF are the combination of adipose-derived stromal cells, endothelial precursor cells, mature endothelial cells, lymphocytes, pericytes, pre-adipocytes, and mature adipocytes (39,40). For bone and cartilage regeneration, the recent advances in the field of molecular and translational medicine have placed SVF at the highest regenerative potential horizon (41). Since they possess MSC-like properties, SVF renders a better regenerative potential, immunomodulation, anti-inflammation, and neoangiogenesis at the site of action (42). Despite the better translational potential of SVF in regenerative medicine, the challenges are viewed in the form of isolation and quantification of cellular components in SVF. Due to the presence of various cellular components in the SVF mixture, adipose-derived stem cells share a common cell surface antigen of hematopoietic stem cell CD34 as proposed by the International Society of Cellular Therapy (ISCT). Various researchers stated that SVF has a strong potential for regenerating tissues like MSCs (38).

SVF mimics the morphology of fibroblasts and possesses MSCs like properties (43). Due to the MSC-like property of SVF, it induces the differentiation of different lineage of cells like osteoblast, chondroblast, myoblast, and adipoblast (44,45). The cellular mixture of SVF possesses cell surface antigens of both HSCs (CD-34 and 45) and MSCs (CD-105 and 146) (46). SVF cells share common cell surface antigens of bone marrow-derived MSCs such as CD-24, 29, 31, 44, 45, 71, 90, 105/SH2, and SH3 (47). Since adipose tissue contains various components of a cellular mixture, the concept of allogenicity with adipose tissue-derived stem cells is questionable. AD-MSCs exhibit significant osteogenic potential with the cytokines secreted by the cellular mixture and hence act as a promising therapeutic agent for bone and cartilage engineering in orthopedic disorders (48). Our recent meta-analysis found AD-MSCs to have an upper hand compared to BM-MSCs in the management of OA knee in terms of their efficacy and safety (49).

Synovium derived MSCs (Sy-MSCs)

MSCs in synovial fluid are increased along with degenerated cartilage in OA and the gene profile of these cells is more similar to the synovial MSCs indicating their role in OA (50). In humans, MSCs derived from synovial tissue may have superior chondrogenic potential (51). In a study, the transplantation of synovial MSC resulted in full defect filling of the cartilage without any adverse clinical events (52). Animal models have revealed that the joint microenvironment has endogenous populations of synovial MSCs which have chondrogenic differentiating potential and to some extent, contribute to cartilage repair (53). Mak and colleagues demonstrated that intra-articular injection of autologous or allogeneic synovial MSCs has beneficial effects when infused into a diseased joint (54). Delgado-Enciso and colleagues recently recommended an inventive approach for cartilage regeneration which is based on the intra-articular injection of bioactive cell-free formulation (BIOF2), a compound that could promote expansion and chondrogenic differentiation of endogenous populations of synovial MSCs (55). Horie and Mizuno reported that Sy-MSCs injected into rat knees accommodated themselves to the lesion, differentiated into chondrocytes directly, and promoted cartilage regeneration without traveling to distant organs (56,57). Repeated injections of Sy-MSCs have shown a chondroprotective effect and promising results in rat OA models (58). Successful cartilage repair following direct injection of Sy-MSCs may reflect the ability of synovial MSCs to home to chondral lesions.

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Endometrium derived MSCs (En-MSCs)

En-MSCs drew attention from global researchers for their accessibility from the source and non-posting ethical issues. In a reproductive life cycle of a woman, the endometrium undergoes over 400 cycles of regeneration (59). En-MSCs pose a greater potential for chondrogenesis via TGF-β, FGF-2, -9 & -18 and IGF-1 (60). The isolation of En-MSCs is through the collection of menstrual blood, hysterectomized specimens, or endometrial biopsy. En-MSCs possess OCT-4 (61), SSEA-4 (62), and CD49a (63) but lacks STRO1 expression (64,65). En-MSCs exhibited higher colony-forming units and proangiogenic properties than BM-MSCs (63). Alcayaga-Miranda *et al*. exhibited that En-MSCs produce less cytokine activation and immunosuppressive molecules than BM-MSCs (63). Wolff *et al*. demonstrated chondrogenic differentiation potential in En-MSCs (66). Evidence proved the presence of epithelial cell nests in the endometrium which further shown stromal-epithelial interaction for differentiation into cells of bone, cartilage, and adipose tissue (67). Chen and his colleagues proved the inferior potential of En-MSCs towards chondrogenic and osteogenic nature when compared with BM-MSCs and Pl-MSCs (68,69).

Placental derived MSCs (Pl-MSCs) & umbilical cord derived MSCs (Um-MSCs)

The appeal of using Umbilical cord-derived stem cells and placenta-derived stem cells is that they are the youngest stem cells available for OA treatment. They are considered "Day Zero Cells" (70). Umbilical cord blood as well as umbilical cord tissues contain cells with good proliferative capacity and chondrogenic potential. Also harvesting these cells is a painless and non-invasive procedure (71). Recently, clinical outcomes of human UCB-MSCs (hUCB-MSCs) for cartilage regeneration have been reported (72). In a trial, it was seen that a single intra-articular injection of placental MSC derived allogenically resulted in significant symptomatic improvement as well as improvement in the thickness of cartilage in knee OA (73). Khalifeh Soltani *et al*. reported that an allogenic placental MSC-based product appeared safe and effective for the regeneration of hyaline-like cartilage in OA of the knee after 24 weeks of follow-up, obtained favorable clinical outcome (74). At the end of 24 weeks follow-up, they observed 10% improvement in cartilage thickness in the intervention group. Wang *et al*. found that Warton jelly-MSCs secreted more Glycosaminoglycans than did BM-MSCs during chondrogenic differentiation (75). A study showed the repair of articular cartilage in animal models with the help of placenta-derived MSCs grown on silk fibroin material (76). Human umbilical origin stem cells are found to mitigate OA progression in large animal models too (77). In the phase I/II trial, a repeated UC-MSC dose strategy led to a favorable safety profile and improved clinical results for the treatment of long-term pain in knee OA patients (78).

Amniotic fluid derived MSCs (AF-MSCs)

The applications of amniotic fluid-derived MSCs have proven and hold a wide range of promising healing effects in sports injuries and pathologies of bone, tendon, and cartilage disorders. AF-MSCs have a higher differentiation potential for osteogenic and chondrogenic lineage than adult stem cells (79). AF-MSCs confer a low risk of tumor development without catering to the ethical concern and epigenetic memory over ESCs (80). *In vitro* studies suggest that the amniotic membrane proved to be a scaffold for cellular therapy in cartilage tissue repair. Preclinical studies suggested that dehydrated human amnion chorion membrane act as a disease modifier in OA knee (81,82). Attenuation of cartilage degeneration has been proved with a minced amniotic membrane in a rat MMT OA model (83). Willett *et al*. injected a dehydrated human amniotic membrane for the management of OA knee in the rat model and found lowered cartilage attenuation with enhanced proteoglycan and collagen II content in the regenerated cartilaginous tissue (84). In the literature, only two clinical trials on amniotic fluid-derived MSCs for management of OA knee were available. Vines *et al*. and Farr *et al*. proved the safety, efficacy, and functional outcome of amniotic fluid-derived MSCs on the management of OA knee in various KL grades (85,86).

Peripheral blood derived MSCs (PB-MSCs)

An increasing number of studies have suggested that PB is a potential alternative source of MSCs, which have shown similar chondrogenic differentiation potential with bone marrow-derived MSCs (BM-MSCs) in both *in vitro* and *in vivo* studies (87,88). In a series of studies performed by Saw *et al*., a significant amount of articular cartilage regeneration, as well as profound symptomatic relief, was seen with autologous PB progenitor cells (89,90). In a clinical trial published in the year 2017, it was cited that

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intra-articular injection of allogenically harvested PB stem cells combined with hG-CSF helped in alleviating pain, disability, and better cartilage regeneration in OA patients and avoided TKA in these patients offering a safe and exciting possibility in the treatment of OA (91). A study by Skowroński showed superior results for cartilage regeneration by PBMSC as compared to bone marrow-derived cells (92). Another study demonstrated good evidence of articular cartilage repair, an increase in cartilage thickness as well as enhanced physical function by use of repeated injections of PBSC into the damaged joint (93). A recent review article established the use of PBMSCs in cartilage repair and regeneration to be very safe and efficacious (94). In phase II clinical trial on the use of PBSCs in an arthritic knee, it was found that these cells increase the mean cartilage thickness and improve the quality of life (95).

Ethical concerns

With the rapid advances in regenerative medicine using stem cells, ethical concerns for their use on patients have also been more stringent (96). The ethical issues that all stem cell researchers face begin with the development of a meaningful question before the clinical translation of the technology in hand which might bring about an answer which is both scientific and social value (97). The risk and benefits of the therapy to society and patients must be balanced at each stage of their research (98). Sound justification is needed to upgrade the research from animal models to human subjects (99). Minimizing the risk and harm, appropriate selection and recruitment of the subjects, and making an informed decision through consent forms are the ethical considerations involved in any clinical research, and stem cell therapy is no exception (100,101). With the increase in concerns for the use of animals in preclinical research, good animal models are often inadequate to equate the effects in humans. Hence, an uncertainty continues in the first human trials using stem cells even with increased safety protocols are in place (102).

Comparative characteristics of the individual sources and the level of ethical consideration with the sources and significance are elaborated in *Table 1*.

Ongoing research & future directives

Several preclinical studies and clinical trials have revealed that mesenchymal cells can be used to treat OA knees because of their self-renewal property and capacity for differentiation into the functional chondrocytes to form cartilage tissues, release various cytokines & chemokines, and provide an appropriate conducive microenvironment to promote cartilage repair (103).

Although the reliability of such treatment methodology for OA knee is being tested in human subjects by a few clinical trials, they provide us with conflicting results and thereby clouding this only ray of hope for OA knee patients (104). To date, 87 trials have been registered in the clinical trials registry, with 57 ongoing trials and 29 completed trials with their protocols given in *Table 2*.

Future directives

Globally, regenerative science in orthopedics holds the future to treat certain conditions where clinicians face stagnation and challenges in the available treatment modalities for certain diseases such as the moderate stage of progressive OA, uncontrolled rheumatoid arthritis, avascular necrosis of the head of the femur, tendinopathies, delayed and non-union of fractures, etc. (105). Stem cells and regenerative medicine hold positive health outcomes in various orthopedic disorders, which have a wide range of osteogenic and osteoinductive potentiality (4-7). Various researchers have worked on the next generation of platelet-rich plasma-like allogenic platelet lysate, platelet-rich fibrin, and various types of MSCs (8-11).

The scope for further research in platelet-rich plasma and MSCs in OA relies on standardization of dosage and frequency of the injection, universal protocol on preparation methods and injection techniques, quantification of growth factors injected, the role of autologous or allogenic preparation, radiological documentation on cartilage growth, preparation and standardization for allogenic formulation and conduction of randomized controlled trials to compare the efficacy and safety of various sources of MSCs and between other methods of cellular therapy in OA knees.

Conclusions

Currently, various qualitative clinical measurements used to assess the outcomes of various sources of MSCs used in OA knee does not give an objective assessment of their efficacy. The development of appropriate surrogate systems of comparative design with more sensitive quantitative methods of outcome assessment to establish a comparative

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Table 1 Comparative characteristics of the varied sources of MSC therapy for OA knee

Sources of MSCs	Ethical consideration	Sources	Significance	Invasiveness
ESCs	+++	Inner cell mass	Totipotent in nature; ? Allogenicity	–
BM-MSCs	+	Iliac crest	↑ Potential to regenerate bone and cartilage; Easy to isolate stem cells; Auto & allogenicity ++; No culture required	++
AD-MSCs	+	Abdomen, medial aspect of thigh	↑ potential to regenerate cartilage & soft tissues; Complex natured to isolate stem cells; Autologous ++; ??? Allogenicity	++
Sy-MSCs	+	Synovium around knee joint	↑ Potential to regenerate bone and cartilage; Auto & allogenicity ++; Culture required for exponentiation	+
En-MSCs	+	Endometrial shedding	Potent to regenerate bone and cartilaginous tissues; Allogenicity ++; Culture required	+
Pl-MSCs	+	Amniotic membrane, chorionic plate, chorionic villi, decidua	Pluripotent in nature; Difficult to isolate cell mass; ↑ potential to regenerate bone, cartilage & soft tissues; Auto & allogenicity ++	–
Um-MSCs	++	Umbilical cord, Wharton's jelly	Pluripotent in nature; Auto & allogenicity ++; Culture required	–
AF-MSCs	+	Cytotrophoblast, syncytiotrophoblast	Pluripotent in nature; Auto & allogenicity ++; Culture required	–
PB-MSCs	+	Circulating mononuclear cells	Enhanced osteogenic and adipogenic potential	+

+, low; ++, medium; +++, high; –, non-invasive (allogenic); ???, doubtful; ↑, increased. ESCs, embryonic stem cells; BM-MSCs, bone marrow derived MSCs; AD-MSCs, adipose tissue derived MSCs; Sy-MSCs, synovium derived MSCs; En-MSCs, endometrium derived MSCs; Pl-MSCs, placental derived MSCs; Um-MSCs, umbilical derived MSCs; AF-MSCs, amniotic fluid derived MSCs; PB-MSCs, peripheral blood derived MSCs.

efficacy of various sources is the need of the hour. The available literature is limited to qualify a source to be ideal for clinical use in humans in OA knee. A consistent methodology to objectively evaluate the efficacy and safety of various sources of MSCs has to be utilized in all clinical trials to conclude their comparative effectiveness and safety.

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Table 2 Completed clinical trials evaluating the role of MSC in the management of osteoarthritis knee with published results

Sl. No.	Author	NCT No.	Year	Country	MSC source	Cell density	Total patients	Follow up	Clinical trial phase
1	de Girolamo *et al*.	NCT01485198	2010	Mexico	Autologous hematopoietic stem cells from bone marrow	10 mL BMAC	61	6 months	I
2	Taghiyar *et al*.	NCT00850187	2012	Iran	Autologous cultured BM-MSCs	–	6	12 months	I
3	Emadedin *et al*.	NCT01207661	2012	Iran	Autologous cultured BM-MSCs	5×10^5 cells/kg/body weight	6	12 months	I
4	Shadmanfar *et al*.	NCT01873625	2013	Iran	Autologous BM-MSCs	–	60	6 months	II & III
5	Sheinkop	NCT01601951	2014	USA	Autologous BMAC	–	12	12 months	I
6	Pers YM *et al*.	NCT01585857	2014	France	Autologous AD-MSCs	$2/10/50\times10^6$ AD- MSCs	18		I
7	Vives *et al*.	NCT01227694	2015	Spain	Autologous cultured BM-MSCs	40×10^6 MSCs	15	12 months	I & II
8	Orozco *et al*.	NCT01183728	2015	Spain	Autologous BM-MSCs	40×10^6 MSCs	12	24 months	I & II
9	Orozco *et al*.	NCT01586312	2015	Spain	Allogenic *ex vivo* cultured BM-MSCs	40×10^6 MSCs	30	12 months	I & II
10	Al-Najar *et al*.	NCT02118519	2016	Jordan	Allogenic *in vitro* cultured BM-MSCs	$61\times10^6\pm0.6\times10^6$ MSCs	13	12 months	II
11	Pham *et al*.	NCT02142842	2016	Vietnam	Autologous SVF and PRP	SVF—1.0 to 5.0×10^7 cells	30	18 months	I & II
12	Ghani *et al*.	NCT01448434	2016	Malaysia	*Ex vivo* cultured adult allogenic MSCs	–	72	12 months	II
13	Agarwal *et al*.	NCT01453738	2016	India	*Ex vivo* cultured allogenic BM-MSCs	$25/50/75/150\times10^6$ cells	60	12 months	II
14	Royan Institute	NCT01504464	2016	Iran	MSCs	–	40	3 months	II
15	Chen PJ	NCT02291926	2017	China	Human UC-MSCs	2×10^7 hUC-MSCs	20	12 months	I
16	Camilleri *et al*. and Shapiro *et al*.	NCT01931007	2017	USA	Autologous BMAC	5 mL of treated cells + 10 mL platelet poor bone marrow plasma	25	12 months	I
17	Lamo-Espinosa *et al*.	NCT02123368	2017	Spain	Autologous *ex vivo* cultured BM-MSCs	10×10^6 cells	30	12 months	I & II
18	Song *et al*.	NCT01809769	2017	China	Autologous AD-MSCs	$1/2/5\times10^7$ cells/3 mL	18	24 months	I & II
19	Bao and Zhang	NCT02162693	2017	China	Autologous *in vitro* extended AD-MSCs	–	53	12 months	II
20	Lim *et al*.	NCT01041001	2017	Korea	CARTISTEM allogenic UC-MSCs	Single dose of 500 μL/cm^2 containing 2.5×10^6 cells	102	60 months	III
21	Lim *et al*.	NCT01626677	2017	Korea	CARTISTEM allogenic UC-MSCs	Single dose of 500 μL/cm^2 containing 2.5×10^6 cells	103	48 months	III
22	Matas and Espinoza	NCT02580695	2018	Chile	Allogenic UC-MSCs	20×10^6 and 3 mL hyaluronic acid	30	12 months	I & II

Table 2 (*continued*)

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Table 2 (*continued*)

Sl. No.	Author	NCT No.	Year	Country	MSC source	Cell density	Total patients	Follow up	Clinical trial phase
23	Ruane	NCT02958267	2018	USA	Autologous BMAC	5–6 mL BMAC	30	12 months	II
24	Cellular Biomedicine group	NCT02641860	2018	China	Autologous *in vitro* extended AD-MSCs	–	22	48 months	I
25	Jas Chahal	NCT02351011	2019	Canada	Autologous MSCs	1/10/50×10^6 MSCs	12	60 months	I & II
26	Lee WS *et al*.	NCT02658344	2019	Korea	Autologous AD-MSCs	1×10^8 cells per 3 mL	24	6 months	II
27	Ho Ki Wai	NCT04326985	2020	Hong Kong	Autologous MSCs	–	20	12 months	I
28	Gary Hieronimus	NCT03337243	2020	USA	Human amniotic membrane and Human umbilical cord & Wharton's jelly injections	–	60	3 months	I
29	Nature Cell Company	NCT02674399	2020	USA	Autologous AD-MSCs	–	28	24 months	II

BMAC, bone marrow aspirate concentrate; BM-MSCs, bone marrow derived MSCs; AD-MSCs, adipose tissue derived MSCs; UC-MSCs, umbilical cord derived MSCs; PRP, platelet rich plasma; SVF, stromal vascular fraction.

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/sci-2020-055). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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