

## Review article

## Narrative review: Mesenchymal stem cells derived from the umbilical cord and osteoarthritis



## Revisión narrativa: células madre mesenquimales de cordón umbilical y osteoartritis

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## ABSTRACT

Osteoarthritis (OA) is the leading cause of articular pain in adult patients, with a high worldwide prevalence and a trend towards increasing. By 2050, 642 million people are expected to suffer from knee OA. Current treatment focuses on measures to prevent progressive joint wear and control symptoms such as pain. Research in regenerative medicine, including the infiltration of platelet-rich plasma, has not yet provided solid evidence for its efficacy. With the advent of cellular therapy, the isolation and expansion of mesenchymal stem cells (MSCs) from various origins have shown promise in reducing inflammation and creating a suitable environment for the regeneration of articular cartilage. This narrative review focuses on umbilical cord-derived mesenchymal stem cells (UC-MSCs), which have certain advantages over other types of MSCs. It summarizes the various clinical trials conducted in recent years, based on a search of multiple databases.

## RESUMEN

La osteoartritis (OA) es una de las principales causas de dolor articular en pacientes adultos, con una alta prevalencia a nivel mundial y una tendencia al aumento. Se estima que para el año 2050, 642 millones de personas padecerán OA de rodilla. En la actualidad, el tratamiento se enfoca en medidas para evitar el desgaste progresivo de la articulación y controlar el dolor. Se ha buscado una respuesta en la medicina regenerativa, como la infiltración articular de plasma rico en plaquetas, aunque hasta la fecha no se ha obtenido suficiente evidencia que respalde su uso. Con el advenimiento de la terapia celular, se ha intentado utilizar el aislamiento y la expansión de células madre mesenquimales (CMM) de diferentes orígenes para la infiltración articular, con el fin de disminuir la inflamación y crear un medio propicio para la regeneración del cartílago articular. En esta revisión narrativa nos centramos en las CMM derivadas de cordón umbilical (CMM-CU), las cuales presentan ciertas ventajas sobre otras CMM, y resumimos los ensayos clínicos de los últimos años, obtenidos mediante una búsqueda en diferentes bases de datos.

## Palabras clave:

 Células madre mesenquimales  
Cordón umbilical  
Osteoartritis  
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## Introduction

Osteoarthritis (OA)—also known as arthrosis, osteoarthrosis, and degenerative joint disease—is the leading cause of chronic joint pain and long-term disability in adults. Its prevalence is increasing: in 2020, it was estimated that approximately 595 million people had some form of

OA, and it has been projected that by 2050, 642 million individuals will have knee OA alone, according to the Global Burden of Disease (GBD) 2021 study [1,2]. Although it is mostly considered a disorder that affects people over 60 years, it is estimated that 3.5% of adults aged 30–60 are also affected [2,3]; it is a disease that is more prevalent in women across all age groups [2].

In knee osteoarthritis, structural changes occur at the joint level, manifesting as pain, functional limitations, poor sleep quality, fatigue, depression, and loss of independence [4]. These symptoms not only af-

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fect the individual's quality of life but also society, due to the burden of the disease and its economic repercussions.

In Colombia, a prevalence study using the COPCORD strategy estimated that approximately 10% of the population suffered OA [5]. Cuervo et al. conducted a disease burden study and found that 3,335,553 people suffered from OA, mostly women between 50 and 59 years of age; eighty-six subjects died, a quarter of whom died from surgical procedures. Disability-adjusted life years (DALYs) were 292.11 per 100,000 inhabitants, lower than for low back pain (606 per 100,000 inhabitants) and higher than for rheumatoid arthritis (192.46 per 100,000 inhabitants) [6].

Concerning the economic burden, direct factors associated with OA include the costs of surgery, hospital resources, caregiver time, pharmacological and non-pharmacological therapy, as well as the cost of complications and adverse effects. Indirect costs encompass lost productivity, absenteeism, and premature mortality, among others [4]. In 2013, OA was the second most costly disorder in the United States, accounting for 4.3% of hospitalization costs, equivalent to \$18.4 billion [7]. In Colombia, to date, no data have been reported.

Several clinical practice guidelines are available for the non-surgical treatment of individuals with knee, hip, hand, or multiple joints OA. Treatment of this disease includes both pharmacological and non-pharmacological measures. Non-pharmacological measures include weight management, especially for joints such as the knee and hip, and exercise programs; the use of orthotics is also recommended [8]. Pharmacological interventions include topical or oral non-steroidal anti-inflammatory drugs (NSAIDs), antidepressants such as duloxetine, and intra-articular corticosteroid injections [8]. American guidelines provide a conditional indication for the use of intra-articular hyaluronic acid injections for knee OA when other interventions are no longer effective [8]. In advanced stages, when pain is not adequately controlled and there is significant functional limitation, joint replacement surgery is performed, whenever possible [8]. The most recent guidelines from the Osteoarthritis Research Society International (OARSI), from 2019, propose a classification of patients into five subgroups, based on predominant comorbidities: without comorbidities, gastrointestinal comorbidities, cardiovascular comorbidities, frailty, generalized pain or depression, to better guide treatment [9].

Because none of these measures address the underlying cause of OA, regenerative medicine has been explored. Platelet-rich plasma (PRP) injections have been used, and studies have shown a benefit in knee OA compared to placebo, specifically in patient-reported outcome measures (PROMs) [10–13]. However, these studies have not assessed knee function or structural changes following PRP use [14]; it is also noted that standardizing the preparation technique for PRP use is difficult [15]. More recently, intra-articular injections of mesenchymal stem cells (MSCs) have been tested as a novel therapeutic alternative [16]. This narrative review is conducted in response to the growing need to find an alternative treatment for OA, targeting the regeneration of joint components, primarily articular cartilage, a mechanism that has already been extensively studied for MSCs in preclinical and clinical models [16], with emphasis on MSCs derived from umbilical cord (UC-MSCs).

## Methods

For this narrative review, an extensive search was conducted in several databases: PubMed, Embase, Scopus, and Ovid, using the MeSH and Emtree terms mesenchymal stem cells AND osteoarthritis. Limiting the search to the last five years, numerous articles were found, from which those published in high-impact journals, systematic reviews, and clinical practice guidelines discussing the background, pathogenesis, and MSC-UC in OA were selected. To search for clinical trials, the term umbilical cord in the same databases was used, looking for manuscripts that were clinical trials or systematic reviews of clinical trials published in the last ten years.

## Pathophysiology of OA

Several risk factors have been identified that contribute to the initiation or progression of primary OA, including obesity, sedentary lifestyle, joint structural factors, and genetics [17]. This indicates that OA is not an inevitable condition of aging [18]. Furthermore, attempts have been made to characterize OA phenotypes according to the main disease mechanism, with more than one potentially coexisting. These phenotypes include chronic pain, joint or biomechanical malalignment, inflammation, metabolic disorders, minimal joint disease, and abnormalities in bone and cartilage metabolism [19].

Initiation and progression factors disrupt the homeostasis of various immune response signaling molecules in the joint. These factors and molecules, in turn, modify the composition and structure of the cartilaginous matrix, leading to cartilage loss and changes in the subchondral bone [20]. It is currently debated whether cartilage loss is a primary process or secondary to a persistent systemic inflammatory state [21]. This cartilage loss perpetuates an inflammatory joint state that promotes ineffective healing and repair, evidenced by replacement with fibrocartilage, abnormal bone formation via osteophytes, alteration of the subchondral bone due to changes in its composition, and synovial inflammation. Ultimately, these processes affect all joint components and alter joint biomechanics [20].

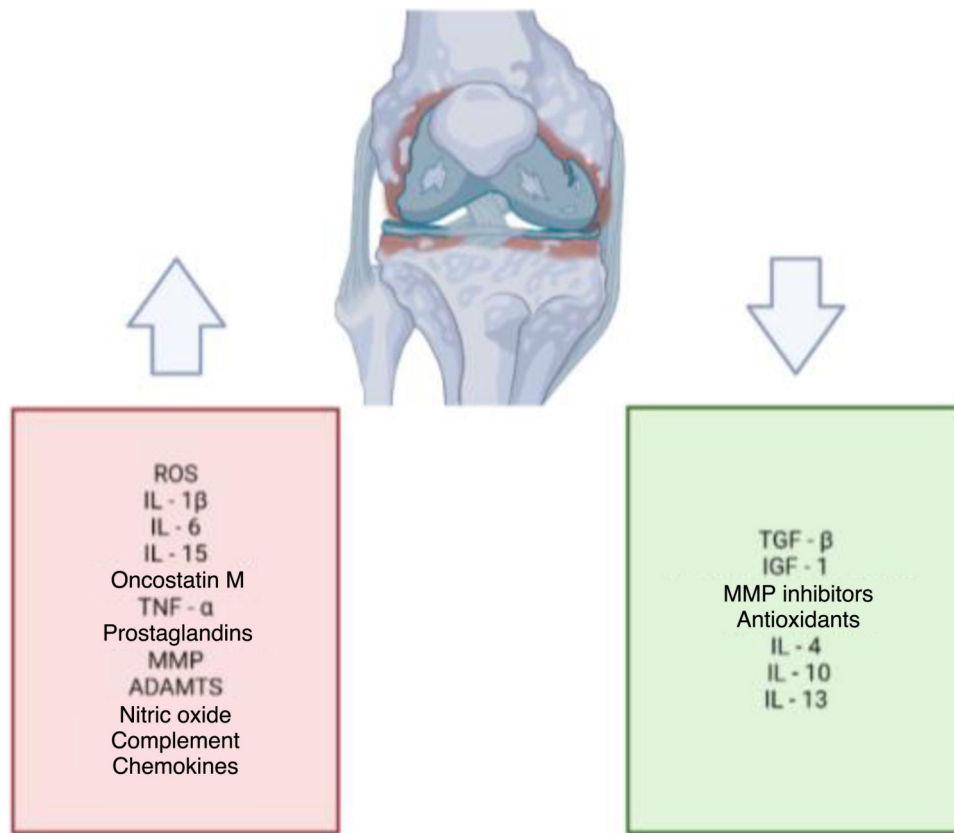
Biomechanical stress, which arises from various factors such as overweight, obesity, or muscle weakness, can cause joint instability and overload. Chronic biomechanical stress induces chondrocytes to release degenerative enzymes via mechanoreceptors [22].

Senescence, which is the irreversible cellular state of suspended growth or cell division in chondrocytes [23,24], is another factor that has been linked to their inability to adequately repair the extracellular matrix (ECM) [25]. Chondrocytes can enter a state of stress-induced premature senescence, in addition to replicative senescence, where there is telomere shortening and increased  $\beta$ -galactosidase activity [26], with a secretory phenotype associated with senescence that differs from its physiological state. In chondrocytes, their secretome, understood as the set of molecules and biological factors that are expelled from a living cell into the extracellular space [27], is normally composed of ECM proteins (proteoglycans and collagen), cytokines (IL-6, IL-8, IL-17 $\beta$ , CCL 2,8,14,20, inhibin- $\beta$ A), growth factors (IGFBP, gremlin-1, chondromodulin and pleiotropin), enzymes (matrix metalloproteinases [MMP] and their endogenous inhibitors [TIMP]) and miscellaneous components (elsolin, clusterin and TGF- $\beta$ ); all these substances and others that make up alterations in secretome in greater or lesser proportion in OA [28].

Another pathological change has also been described when chondrocytes are subjected to mechanical stress: chondrocyte hypertrophy; both this and senescence would be involved in OA [26,29].

Studies have shown the importance of communication between cartilage and subchondral bone. The latter also responds to compression and biomechanical stress [30] and mediates cartilage catabolism via exosomes from osteoblasts to chondrocytes from the early stages of the disease. The *Wnt* pathway, important in regulating osteoblast and osteoclast activation, has been implicated in this communication [18,25,31].

Regarding the molecules in the joint microenvironment, several have been associated with OA, each with either an anabolic or catabolic role. Among the catabolic molecules are reactive oxygen species (ROS) and cytokines such as IL-1 $\beta$ , IL-6, IL-15, oncostatin M, TNF- $\alpha$  and associated transcription factors such as NF- $\kappa$ B, prostaglandins, and proteinases such as MMPs, which can be ADAMTS (A Disintegrin And Metalloproteinase with Thrombospondin type 1 Repeats) and may be called collagenases or aggrecanases, among others, are present. On the other hand, anabolic proteins, such as TGF- $\beta$  and  $\beta$ IGF-1, anti-inflammatory cytokines, and MMP inhibitors are decreased [17,20] (Fig. 1). Leukocyte infiltration occurs mainly in the synovial membrane by monocytes/macrophages, mast cells, natural killer (NK) cells, dendritic cells, B cells, and granulocytes [18,32].



**Figure 1.** Alteration in the balance of different molecules in the joint with OA. Graph created in BIORENDER©.

The molecules that will act as DAMPs (*Damage Associated Molecular Patterns*), and released into the synovial space by the action of the different MMPs, are the components of the ECM (fibronectin, hyaluronan, lubricin, tenascin C, type II collagen), which have an important role in the generated inflammation, since they will activate the innate immune response, specifically to the macrophages in the synovial membrane, through different subtypes of TLR recognition pattern receptors (Toll-Like Receptors), which ultimately promote the release of cytokines and the pro-inflammatory state [18,22].

#### Umbilical cord-derived MSCs

Stem cells are a group that shares features such as immaturity, undifferentiation, and a high proliferation rate. These cells have the capacity for self-renewal, exhibit plasticity, can be transdifferentiated, and have a long lifespan. Transdifferentiation is the process by which a differentiated cell dedifferentiates to a stage in which it can change its lineage [33,34]. There are several types of stem cells in adults: hematopoietic, mesenchymal, among others [35]. (Fig. 2).

MSCs can be of autologous (e.g., adipose tissue or bone marrow) or allogeneic (e.g., perinatal tissues) origin. Concerning perinatal tissues, MSCs can be obtained from the amniotic or chorionic membrane, amniotic fluid, and umbilical cord [36]. Three criteria have been established for their classification: first, they must adhere to plastic when maintained under standard culture conditions; second, they must express CD105, CD73, and CD90 on their surface, but not CD45, CD34, CD14, CD11b, CD79 $\alpha$ , CD19, or HLA class II molecules; third, they must differentiate into chondroblasts, osteoblasts, or adipocytes *in vitro* [37].

Concerning UC-MSCs, these can have different origins. The umbilical cord can be divided into three parts: the amnion, the blood vessels, and Wharton's jelly (WJ). WJ can be further subdivided into the subamnion, intermediate, and perivascular. WJ is a gelatinous connective tissue,

composed mainly of extracellular matrix rich in type I and type II collagen fibers, glycosaminoglycans, proteoglycans, myofibroblasts, and diffuse plasma proteins. WJ supports and protects the umbilical vasculature, preventing its torsion and compression, provides a rich supply of MSCs, and is the allogeneic tissue with the highest concentration of these cells per milliliter [38].

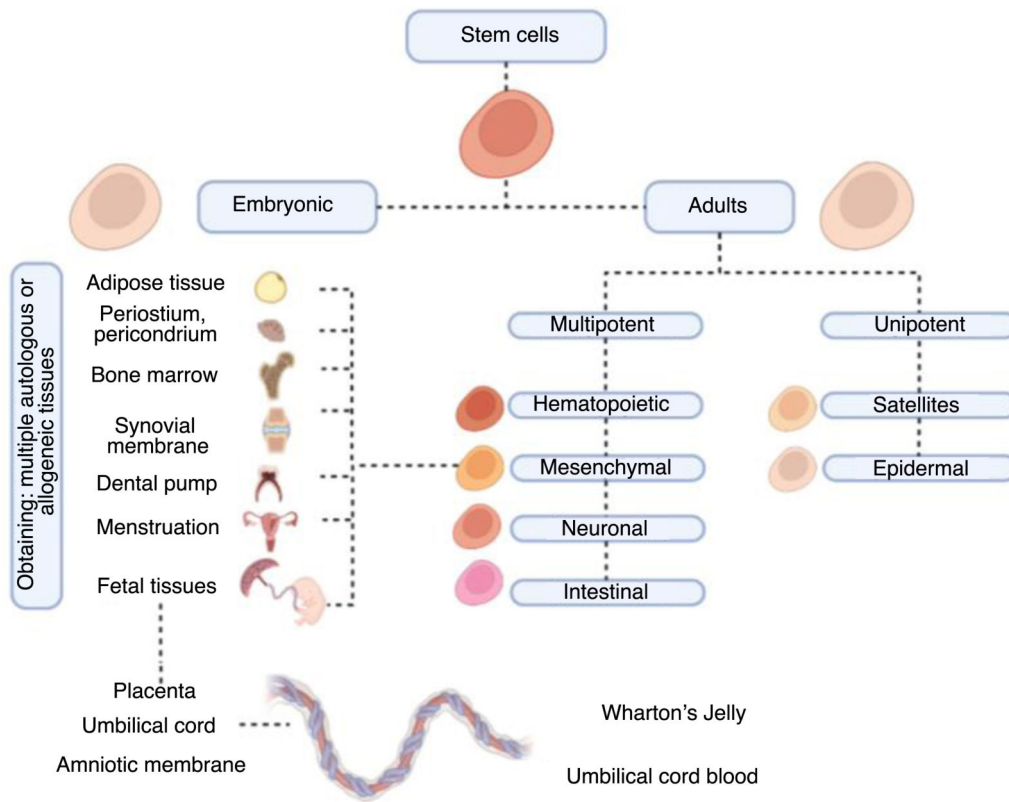
Unlike stem cells from other sources, UC-MSCs offer several potential advantages: their collection does not affect either the mother or the newborn, since the UC is currently considered biological waste and would not raise ethical dilemmas. Additionally, they exhibit fewer DNA mutations, have not been exposed to reactive oxygen species (ROS), are immunoprivileged, and have a high proliferation rate with a high differentiation potential [39].

#### MSCs and OA

It is presumed that MSCs work in different ways in the joint with OA: they differentiate into chondrocytes, exerting immunomodulatory and paracrine functions through their secretome (Fig. 3).

The role of resident MSCs in the joint has been studied. These cells, under normal conditions, respond to the joint microenvironment; in OA, they suppress the activation of the synovial membrane and indirectly prevent damage to the articular cartilage and the formation of osteophytes, through the inactivation of macrophages or the change to a pro-inflammatory M1 phenotype to a restorative/repair M2 phenotype [32,40,41].

Initially, it was thought that their main mechanism of action was differentiation into chondrocytes. When this differentiation is performed *in vitro*, it is induced via a non-natural pathway, leading to the formation of tissue with markers of hyaline cartilage, fibrocartilage, and hypertrophic cartilage, the latter two having inferior mechanical properties. The simplicity of these models is acknowledged, compared to the dif-



**Figure 2.** Origins of MSCs and possible tissues from which autologous or allogeneic MSCs can be obtained. Graphic created in BIORENDER©.

ferentiation that occurs physiologically in the fetus. It is believed that under conditions of OA, this differentiation does not occur because the necessary environment is lacking [21,42,43]. Furthermore, the fate of MSCs after injection has been assessed; multiple animal models in the literature report on intra-articular infiltration [44–46]. For example, in the murine model developed by Toupet et al., they found that only 13% of the MSCs derived from adipose tissue remained at the joint level in the first month, some migrated to niches in bone marrow, adipose tissue, and muscle [47], so in most of the literature, this mechanism of action is called: “hit and run”.

The main effector molecules of MSCs are anti-inflammatory substances such as prostaglandin E2 (PGE2), Transforming Growth Factor beta (TGF-β), indolamine 2,3 dioxygenase (IDO), and TNF-α *Stimulated Gene* (TSG-6). In addition to these substances, the MSC secretome, which has been extensively studied, includes several proteins with anti-apoptotic actions, such as stanniocalcin (STC-1), anti-fibrotic actions, such as basic fibroblast growth factor (bFGF), adrenomedullin (ADM), and hepatocyte growth factor (HGF), and others that are involved in chondrogenesis and immunosuppression [48].

These secretome molecules are also found in extracellular vesicles (ECVs), which are small structures of varying sizes composed of a phospholipid bilayer with multiple cytoplasmic components inside: mRNA, transfer RNA, microRNA, non-coding RNA, circular RNA, mitochondrial DNA, and proteins are all components of exosomes. One type of ECV is the exosome, which measures between 40 and 100 nm [48]. Exosomes are rich in tetraspanins, a family of transmembrane proteins with specific functions, as well as heat shock proteins (Hsp60, Hsp70, Hsp90). Other proteins, such as clathrin, Alix, Tsg101, and proteins from the cell of origin, are also exposed [41,49]. Exosomes have been tested in OA and articular cartilage defects, as they increase the encoding of genes responsible for chondrocyte proliferation and decrease those that induce apoptosis. They offer advantages over mitochondrial cells (MCCs) due to their hypoimmunogenicity, very low risk of rejection, simpler transport

conditions, and improved viability. As with MSCs, there are multiple clinical trials that prove the effectiveness of exosomes in OA; these are not the subject of this review [49].

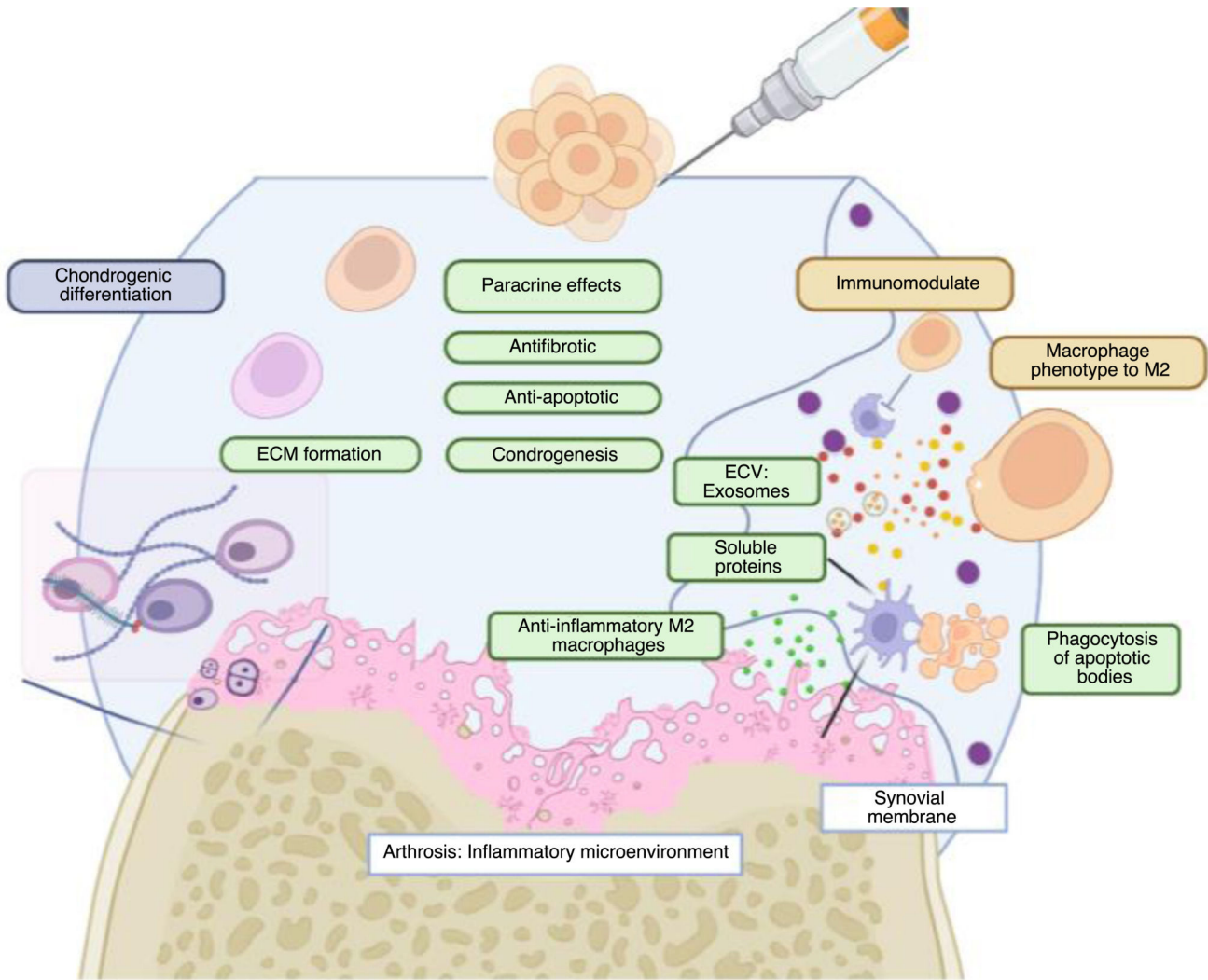
Similarly, efferocytosis (phagocytosis of apoptotic bodies) of MSCs by macrophages generates a phenotype change from M1 to M2. Upon internalization, they do not induce a CD4 + T lymphocyte response, but rather a clonal expansion of regulatory T cells; these macrophages also produce IDO, PGE2, and TGF-β [48].

It is important to emphasize that these cells have hypoimmunogenicity, which has shown them to be well tolerated. When expanded in culture, they express low levels of HLA class I and absence of class II molecules. In response to cytokines such as IFN-γ or during differentiation, they may express higher levels of HLA I and II [44].

On the other hand, immunotolerance has been debated. There is evidence that these cells can be rejected by the host, as observed in the murine model by Eliopoulos et al. In that study, allogeneic bone marrow MSCs were injected subcutaneously into a collagen scaffold. The scaffold status was assessed after 15 days, and infiltration by CD8 + T lymphocytes and NK cells was found. In this experiment, rejection occurred earlier with repeated exposure [50]. The cell’s immunosuppressive capacity is dictated by the microenvironment and systemic levels of inflammation. If these are high, it will be easier for the cell to maintain high anti-inflammatory levels and avoid rejection [44].

Often, these cells are used in combination with biomaterials: their use can enhance their therapeutic effect and increase adherence and survival. Therefore, the function of the biomaterials is to serve as a kind of synthetic cartilaginous matrix. These biomaterials include hydrogels based on fibrin, hyaluronic acid, or polyethylene glycol, as well as collagen or hyaluronic acid scaffolds. These biomaterials must have specific features that guide the cells toward differentiation, in addition to helping protect them and promoting adhesion to the cartilage [51].

Furthermore, the placement of UC-MSCs has been associated with surgical procedures to improve their administration, especially when



**Figure 3.** Mechanism of action of MSCs in OA. Three main mechanisms of action are described: 1. Chondrogenic differentiation; this mechanism is the most debated. 2. Paracrine effects through the release of soluble proteins and extracellular vesicles, and indirectly through the ingestion of apoptotic bodies by synovial macrophages. These factors promote chondrocyte survival, ECM (extracellular matrix) formation, and an antifibrotic effect. 3. Direct immunomodulatory effect through the inhibition of macrophages in the synovial membrane. Graphic created in BIORENDER©. ECV: Extracellular vesicles.

attempting to repair articular cartilage defects. Micropores or microfractures are created in the bone using arthroscopic techniques, or they are implanted during surgeries such as high tibial osteotomy [39].

Globally, there are 12 approved products using MSCs, approved by different agencies and for various indications: nine in Asia, only two by the European Medicines Agency (EMA), and one by the Food and Drug Administration (FDA). Two products have been approved for the treatment of OA. One of them, CARTISTEM<sup>®</sup>, in Korea, has used copper-derived MSCs since 2012, and the other, MESESTROCELL<sup>®</sup>, in Iran, has used bone marrow-derived MSCs since 2018 [52].

### Clinical trials: UC-MSCs and OA

Regarding clinical trials, the difficulty in measuring outcomes in subjects using biologics is evident, as LaPrade et al. have pointed out. Clinical trials should only be conducted once solid preclinical evidence, including experimental and animal studies, is available. Subsequently, both subjective and objective data should be evaluated in human studies [53].

In clinical trials of MSCs and knee OA, subjective data are those reported by patients, or PROM (*Patient-Reported Outcome and Measures*). The most used PROM scales are the Western Ontario McMaster Univer-

sities Osteoarthritis Index (WOMAC), the 36 Item Short Form Survey (SF-36), the Visual Analogue Scale (VAS), and the International Knee Documentation Committee Questionnaire (IKDC) [53].

Regarding objective data, the condition of the joint can be assessed through direct visualization through arthroscopy, or imaging techniques such as radiography, which has a limited role as it does not identify changes in soft tissues; knee magnetic resonance imaging (MRI) is more widely used. Joint biopsies can also be taken to reveal microscopic changes in the different structures. Furthermore, attempts have been made to measure various biomarkers, such as growth factors (IGF, VEGF, FGF), among others, without evidence to support their use in clinical trials or clinical practice [53].

Regarding knee MRI, it is widely used to assess non-ossified articular structures. Different scores have been described that assess changes in the various components of OA and allow for quantitative monitoring. Some of the most used scores are the Whole Organ Magnetic Resonance Imaging Score (WORMS) and, more recently, the Magnetic Resonance Image Osteoarthritis Knee Score (MOAKS) [54,55].

Recently, attempts have been made to incorporate joint ultrasound. Quantitative parameters enable the detection of early signs of cartilage damage, such as collagen fractures and surface alterations. Currently, there is no standardized method for evaluating OA using ultrasound [56].

**Table 1**  
Summary of UC-MSCs clinical trials in patients with knee OA.

Author (year)	Knees (patient)	Average age	Follow-up in months (range)	OA stage due to KL or articular cartilage defect	Comparator/surgery	UC-MSCs Type	Dose	Outcomes obtained	Ref.
Park, 2016	7 (7)	58 (29–77)	72 (12–84)	KL grade III with articular cartilage class 4 ICRS defect	No comparator. Arthroscopic implant with microdrilling	Umbilical cord blood with HA CARTISTEM®	Average $1.5 \times 10^7$ cells ( $1.2\text{--}2 \times 10^7$ ) single dose	Three months, tissue repair in arthroscopy. 6 months, previous VAS 49 to 19, no statistical significance. Twelve months, cartilage-like tissue, and arthroscopy. Three years, MRI high GAG content in regenerated cartilage	58
Matas, 2018	18 (18)	56 (40–65)	12	KL grade I-III	Hyaluronic acid	Wharton jelly, Cellistem®	$20 \times 10^6$ cells, single dose in 9 patients.	A greater improvement was noted in the 2-dose group. At 12 months, and compared to HA: initial VAS 39 to 2.4, statistically significant difference. WOMAC initial 25.6 to 4.2, statistically significant difference MRI: no changes in WORMS at 24 to 48 weeks	59
Dilogo, 2020	57 (29)	58.3 (48–68)	12	KL grade I-IV	No	Not specific, umbilical cord	Two doses in 9 patients initially, and at 6 months $10 \times 10^6$ cells, initial dose accompanied by HA. Then, two additional doses of HA in the second and third weeks	WOMAC decreased from 24.6 to 14.7, without statistical significance. VAS in KL grade III and IV OA decreased from 50 to 33.8 at the 6-month follow-up, with statistical significance. The rest showed a reduction, without statistical significance. MRI in grade subgroups I-II and III-IV grades, trend to improvement of cartilage in T2, especially at 12 months, without statistical significance	60
Song 2020	27 (25)	People over 60	26 (24–31)	Medial compartment OA with articular cartilage defect	No comparator.	Umbilical cord blood with HA CARTISTEM®	Non-specific; it depends on the size of the cartilage defect.	IKDC (24–68), VAS (76 to 12), and WOMAC (57 to 10) showed statistically significant improvement, compared to preoperative.	61

Table 1 (Continued)

Author (year)	Knees (patient)	Average age	Follow-up in months (range)	OA stage due to KL or articular cartilage defect	Comparator/surgery	UC-MSCs Type	Dose	Outcomes obtained	Ref.
Song, 2020	128 (125)	58 (43–74)	36 (25–47)	Grade IV KL of the medial compartment and articular cartilage defect	All patients underwent arthroscopy, microfracture, and high tibial osteotomy No comparator.	Umbilical cord blood with HA CARTISTEM®	Non-specific; it depends on the size of the cartilage defect.	14 patients underwent a second arthroscopy, with evidence of repair of the cartilage defect.  In all 125 patients, improvement of the articular cartilage defect to grade III ICRS or better was achieved. Improvement of WOMAC, IKDC, and VAS pre- and post-procedure, with statistical significance.	62
Chung, 2020	93 (93)	56 (43–65)	20 (12–42)	Grade III KL, defect in the articular cartilage	High tibial osteotomy, microfracture, microdrilling No comparator: Arthroscopy, arthroscopic procedures, OTA, microdrilling	Umbilical cord blood with HA CARTISTEM®	It is not specific; it depends on the size of the cartilage defect.	Improvement in all preoperative scores and in the final follow-up IKDC (39–71), WOMAC (44 to 11), with statistical significance.  49 patients underwent a second arthroscopy, with significant improvement of the cartilage defect	65
Günay, 2022	10 (10)	58 (48–68)	10	Not specified	No	Wharton's Jelly	1 × 10 <sup>8</sup>	Decrease at 12 months in VAS and WOMAC scores, increase in SF-36, with statistical significance. Elevated concentration of inflammatory cytokines in synovial fluid	63
Matas, 2024	40 (40)	± 54	6	Grade II-III KL	No	Wharton jelly, Cellistem®	Three groups:  Low dose: 2 × 10 <sup>6</sup> Medium: 20 × 10 <sup>6</sup> High: 80 × 10 <sup>6</sup>	Decreased VAS and WOMAC, especially in the low and medium dose groups, with statistical significance. No changes in MRI in WORMS score	64

HA: Hyaluronic Acid; UC-MSCs: Umbilical Cord-derived Mesenchymal Stem Cells; GAG: Glycosaminoglycans; ICERS: International Cartilage Repair Society; KL: Kellgren-Lawrence OA radiological classification; OA: Osteoarthritis; MRI: Magnetic Resonance Imaging; WOMAC: Western Ontario McMaster Universities Osteoarthritis Index; WORMS: Whole Organ Magnetic Resonance Imaging Score.

**Table 2**  
Reported adverse effects associated with therapy.

Adverse effects	Mild-moderate		Severe	Ref.
Park, 2016	5	Arthralgia (2) Back pain Bladder distension Elevated antithyroglobulin	0	58
Matas, 2019	8	Acute joint effusion	0	59
	4	Pain		
Dilogo, 2020	0	None reported	0	60
Song, 2020	0	None reported	0	61
Song, 2020 (25 patients)	0	None reported	0	62
Chung, 2021	0	Self-limiting joint inflammation (some patients; no number mentioned)	0	65
Günay, 2022	3	Synovitis	0	63
Matas, 2024	40	All patients reported some degree of post-injection pain greater than 40 VAS in 40% of low doses and 100% of high doses.	0	64

Table 1 summarizes the main clinical trials found on the use of UC-MSCs in knee OA over the last ten years [57–64]. Several key points can be drawn from the analysis of the studies summarized in this table. All studies show improvement in the different pain and functional scales described, although these may or may not be statistically significant. Four of the eight studies evaluate changes in MRI, reporting stability or a trend toward improvement, without this being objectively demonstrable [57–59,63].

Four of the eight studies conducted in Asian countries [57,60,61,64] combine surgical therapy for medial compartment OA and correction of varus deformity with the placement of medial compartment microcubitus cartilage grafts (UC-MSCs) using arthroscopy and microdrilling. This intervention is considered successful, as it achieves macroscopic improvement in articular cartilage defects, although histological verification is not performed for fear of damaging the reconstructed cartilage. These three studies do not use a comparator group.

In four of the eight Asian studies mentioned, the product used was CARTISTEM® [57,60,61,64], which is approved by the Korean Food and Drug Administration (KFDA). It is a preparation of UC blood MSCs with hyaluronic acid hydrogel [52]. One of the studies used for the approval of this therapy was the phase III study by Lim et al., in 89 individuals with full-thickness articular cartilage defects, i.e., grade 4, according to the International Cartilage Repair Society (ICRS) score, with or without OA. The therapy was evaluated using UC-MSCs implanted via mini-arthrotomy versus microfracture, and at 48 weeks, an improvement to an ICRS grade 1 defect was found in 97% of patients in the MSCs group, compared with 71% in the microfracture group without UC-MSCs, a statistically significant difference; the assessment of the VAS, WOMAC, and IKDC scales was similar at the 48-week follow-up. During the three and five years of follow-up, there was a statistically significant improvement in the UC-MSCs group versus microfracture [65].

Additionally, the recent publication by Matas et al. [63] is highlighted, which describes the implementation of an animal model and human studies aimed at assessing different doses of UC-MSCs in terms of efficacy and safety. In the murine model, high and low doses were evaluated, and an improvement in histological OA was observed in mice injected with UC-MSCs, in contrast to mice with OA, with no difference between the two dose groups. Furthermore, different inflammatory markers were measured in the lymph nodes of the mice, and a lower number of Th1 and Th17 lymphocytes was found. The human study concludes that low to moderate doses ( $2 \times 10^6$  and  $20 \times 10^6$ ) are more effective and better tolerated, as high doses are associated with greater pain, probably related to inflammation due to the high concentration of cells [63].

In all these studies, it is important to emphasize that the analyzed populations are heterogeneous in terms of age, OA grades, body mass index (BMI), and comorbidities [57–64]. In those studies treating arti-

cular cartilage defects, the number of cells injected in each subject is not mentioned [57,60,61,64]. Furthermore, although the cells are derived from umbilical cord blood, they are extracted from different sites within the cord, such as blood or WJ. Additionally, there is no standardized method for the expansion and production of MSCs. In most studies, the cells are used in conjunction with hyaluronic acid hydrogel in the preparation.

#### Adverse effects

The meta-analysis by Wang et al. [66], for both intravenous infusion and local injection of MSCs over the past 15 years in approximately 20 disorders, reports that the most frequent adverse events following administration are fever, local injection site reaction, constipation, fatigue, and insomnia. The authors conclude that administration is safe [66]. In the systematic review by Baranovskii et al. [67] on the use of MSCs in different indications, both intravenous and local administration are associated with serious adverse reactions: organ fibrosis, thromboembolic disease, and use-related immunosuppression. However, they emphasize that most clinical trials report minor adverse events and that MSCs are generally considered safe [67].

Regarding neoplasms, a potential risk for their development was considered, specifically for MSCs, due to the production of proangiogenic factors; however, only one study [68] has been reported that links the administration of MSCs and the recurrence of hematological neoplasms, which is considered a very rare complication, emphasizing the need for a complete history and contraindicating its use in individuals with active neoplasms [35].

It is also highlighted that adverse effects will also be associated with the MSC expansion technique, since this process can present changes in cell morphology, physiology, and the profile of expressed genes; likewise, during these processes, there may be a greater risk of contamination with microorganisms and xenobiotics [35].

Table 2 depicts the adverse effects reported in the clinical trials summarized in Table 1 for intra-articular injection of UC-MSCs and knee OA. In none of the eight clinical trials, even though four of them [57,60,61,64] were accompanied by surgical procedures, were any serious events reported; nor was any tumor mass growth evident in revision arthroscopy or imaging studies during follow-up.

At the time of writing, in Colombia, intra-articular infiltration with stem cells (SCs), whether autologous or allogeneic, is already available using different cell concentrations and preparation methods. Clinical trials have been conducted with the Cellistem® OA preparation from the Chilean laboratory Cells for Cells [69], but no publications on this topic were found. A search of Clinical Trials revealed no records of trials currently underway in Latin America or Colombia.

## Conclusions

Osteoarthritis affects many people worldwide, in different joints, and causes a high burden of disease and disability. Its prevalence is expected to increase with the aging population.

Like Platelet-Rich Plasma, autologous or allogeneic stem cells offer an option for treating osteoarthritis that aims to promote regeneration and reduce inflammation. Their usefulness has already been tested, initially in animal models, and they have proven effective.

Regarding the reviewed clinical trials, due to the heterogeneity in the presentation of osteoarthritis, the different methodologies and preparations of microvascular monomer used can contribute to significant variability in the results. However, a trend toward improvement in pain and functional scores is observed after infiltration of different doses of microvascular monomer in knee osteoarthritis.

Following this review, we believe there is still a gap in knowledge regarding the use of this therapy. Regarding patients, it is not yet clear which type of subject would benefit; early-stage osteoarthritis differs from advanced-stage osteoarthritis. We consider it appropriate for individuals in whom the structural damage is not severe. Furthermore, the scales for measuring outcomes are not yet standardized. Regarding mesenchymal stem cells, it should be determined whether they should be combined with a biomaterial such as hyaluronic acid, incorporated into a scaffold such as collagen scaffolds, or surgically implanted. Exosomes or extracellular vesicles are another option that requires further investigation. However, many individuals would benefit from these innovative therapies.

## CRedit authorship contribution statement

All authors have contributed to the development of this manuscript. Their contributions include the conception of the idea, the design of the study, the execution of the research, and the acquisition, analysis, and interpretation of data. Furthermore, all authors participated in the drafting of the manuscript and its critical revision, making relevant intellectual contributions. Each author has approved the final version submitted for publication, agreed to the submission of the article to this journal, and assumes full responsibility for the integrity and accuracy of its content.

## Ethical considerations

The study complied with the international standard of the Declaration of Helsinki and the Colombian standards decreed by Resolution 8430 of 1993. It is a study classified as having minimal risk, given that it is a narrative review of literature.

## Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used Copilot AI to improve the writing and readability of the document.

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## Declaration of competing interest

None.

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