

SYSTEMATIC REVIEW

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Human umbilical cord mesenchymal stem cells promoting knee joint chondrogenesis for the treatment of knee osteoarthritis: a systematic review

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Abstract

Purpose The onset of OA is affected by a variety of factors, which eventually lead to the loss of cartilage in the joints, the formation of osteophytes, the loss of normal knee mobility, and pain and discomfort, which seriously affects the quality of life. HUC-MSCs can promote cartilage production and have been widely used in research in the past decade. This article systematically summarizes that it is well used in basic research and clinical studies to promote inflammatory chondrogenesis in the treatment of OA. Provide a theoretical basis for clinical treatment.

Patients and methods This study collected CNKI, Wanfang, PubMed, and articles related to the treatment of OA with HUC-MSCs since their publication, excluding non-basic and clinical studies such as reviews and meta-analysis. A total of 31 basic experimental studies and 12 clinical studies were included. Systematically analyze the effects of HUC-MSCs on inhibiting inflammatory factors, promoting chondrocyte production, and current clinical treatment.

Results HUC-MSCs can reduce inflammatory factors such as MMP-13, ADAMTS-5, IL-1 β , IL-1, IL-6, TNF- α , induced conversion from M1 to M2 in OA to protect cartilage damage and reduce OA inflammation. Synthesize ColIII, SOX9, and aggrecan at the same time to promote cartilage synthesis.

Conclusion HUC-MSCs not only have typical stem cell biological characteristics, but also have rich sources and convenient material extraction. Compared with stem cells from other sources, HUC-MSCs have stronger proliferation, differentiation, and immune regulation abilities. Furthermore, there are no ethical issues associated with their use. Safety: Primarily attributed to pain, the majority of individuals experience recovery within 24 h following injection. HUC-MSCs possess the ability to alleviate pain, enhance knee joint function, and potentially postpone the need for surgical intervention in both non-surgical and other cases, making them highly deserving of clinical promotion and application.

Keywords Osteoarthritis, Knee, Chondrocytes, Regenerative medicine, Exosomes, Safety, Inflammation

Introduction

Knee osteoarthritis (OA) is a chronic disease in which aging or external stimulation leads to degenerative changes of the knee joint [1]. The early clinical manifestations are joint swelling, pain, and limited movement. In the late stage, subchondral hyperplasia occurs, osteophytes form, the knee joint space narrows, and the functional structure of the knee joint undergoes

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changes. The main pathological manifestations were cartilage injury of knee joint, synovial hyperplasia, and abnormal hyperplasia of subchondral bone. Articular cartilage injury is most common in patients with OA. The peculiarities of the articular cartilage structure determine its poor self-repair after injury. Therefore, the treatment of OA cartilage injury is a wide range of clinical difficulties, and also the main cause of restricted knee activity in the elderly [2]. It is estimated that at least 10% of people over the age of 60 worldwide have OA. As the world's population ages, OA patients will continue to increase [1]. The global prevalence of OA among people aged 50 years and older is 14%-38% in women and 4-14% in men. The prevalence of the disease is expected to rise due to increased risk factors such as obesity and advanced age. OA has been linked to genetic factors, mechanical stress, and chondrocyte differentiation. While it is predominantly seen in individuals aged 65 and older, there has been a noticeable increase in its prevalence among those under 65 in recent times [3]. Numerous studies have provided evidence that intra-articular injections of various substances, such as sodium hyaluronate, glucocorticoids, platelet-rich plasma, and stem cells, can effectively decrease systemic side effects and provide more targeted and direct effects by delivering drugs directly into the affected joint. Compared to oral NSAIDs and other systemic pharmacological treatments, local injection therapy has been shown to be more effective [4].

With the continuous discovery of novel biological cells, nanomolecules, cell molecules, and biomaterials, an increasing number of innovative cellular types are being progressively utilized in various branches of medicine [5]. For instance, human umbilical cord mesenchymal stem cells (HUC-MSCs) have found application in diverse medical domains [6]. HUC-MSCs not only have typical stem cell biological characteristics, but also have rich sources and convenient material extraction. Compared with stem cells from other sources, HUC-MSCs have stronger proliferation, differentiation, and immune regulation abilities, and there are no ethical issues [7]. HUC-MSCs are obtained through subculturing neonatal umbilical cord specimens, typically involving the propagation of stem cells over 3-5 generations [8]. HUC-MSCs have been widely used in the treatment of OA in the past decade of research [9]. And it has achieved good results in promoting articular cartilage in cell experiments, animal experiments, and clinical studies [10]. HUC-MSCs can not only differentiate into chondrocytes to promote the generation of joint cartilage, but also secrete a large number of cytokines to participate in the inflammatory immune regulation process, making HUC-MSCs an ideal seed cell for treating OA cartilage injury [11].

Material and methods

This study uses "Osteoarthritis" and "Mesenchymal Stem Cells" as the main search terms, Using "Osteoarthritis," "Osteoarthritis," "Osteoarthroses," "arthritis generative," "Degenerative Arthritis," "Degenerative Arthritis," "Arthrosis," "Arthroses," "Osteoarthris Deformans" and "stem cell mesenchymal," "Mesenchymal Stem Cell," "Bone Marrow Mesenchymal Stem Cells," "Bone Marrow Mesenchymal Stem Cells' Cell," "Bone Marrow Stromal Cells," "Bone Marrow Stromal Cell." The secondary search terms include "bone marrow stromal cells multipotent," "Multipotent Bone Marrow Stromal Cell," "Multipotent Bone Marrow Stromal Cells," "advertisement derived mesenchymal stem cells," "advertisement derived mesenchymal stem cells," "advertisement derived mesenchymal stromal cells," and "advertisement derived mesenchymal stromal cells." Searches were conducted on PubMed, CNKI, Wanfang, and other databases.

Results

Selection of articles

CNKI, Wanfang, PubMed, and articles related to the treatment of OA with HUC-MSCs since their publication until April 1, 2023, were collected, excluding non-basic and non-clinical studies such as reviews and meta-analysis. A total of 31 basic experimental studies and 12 clinical studies were included (Fig. 1). Systematically analyze the effects of HUC-MSCs on inhibiting inflammatory

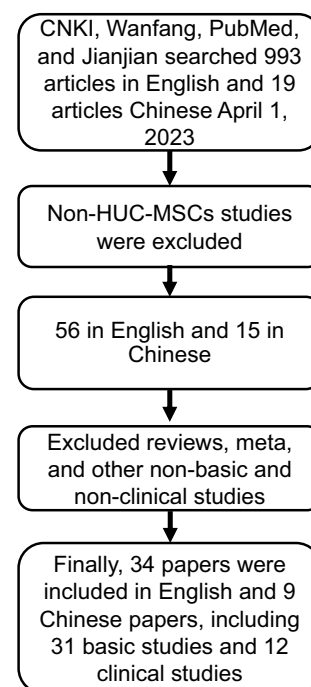


Fig. 1 Flowchart for the identification and selection of studies

factors, promoting chondrocyte production, and current clinical treatment. Explain the relevant mechanisms and clinical effects of HUC-MSCs in treating OA. Analyze the advantages and disadvantages of HUC-MSCs in treating OA, as well as their safety in treating OA. Provide a systematic reference for the clinical use of HUC-MSCs in the treatment of OA. Contribute to guiding clinical treatment, reducing pain in OA patients, avoiding joint function loss, and improving quality of life.

Study characteristics

This study systematically summarizes the mechanism of HUC-MSCs promoting chondrogenesis in the treatment of OA, as well as the clinical treatment results, and draws a table. And analyze the adverse events in the clinical treatment of HUC-MSCs. Provide a new approach for further clinical treatment of OA.

The mechanism of action of HUC-MSCs on chondrocytes

Inhibiting OA inflammatory factors

The occurrence of OA is inseparable from the interaction of various inflammatory factors. HUC-MSCs inhibit the expression of matrix metalloproteinase 13 (MMP-13), collagen X (colx), and cyclooxygenase-2 (COX-2) in OA chondrocytes and enhance the proliferation of OA chondrocytes. Stimulate the expression of type II collagen (Col2), SRYbox9 (SOX9), and aggrecan, promoting the differentiation of HUC-MSCs into chondrocytes. Under certain induction conditions, HUC-MSCs observed osteogenic, chondrogenic, and adipogenic differentiation. HUC-MSCs improved the proliferation of OA chondrocytes and downregulated the expression of inflammatory cytokines, while OA chondrocytes promoted MSCs to differentiate into chondrocytes [5]. Human chondrocytes can withstand hypoxia and environmental conditions for more than 4 days and 10 days, respectively, after aggregation to form spherical bodies [6]. In a study of OA rats

induced by sodium iodoacetate (MIA), local injection of HUC-MSCs significantly improved cartilage erosion and reduced Mankin score. The number of chondrocytes on the surface of articular cartilage was also significantly increased, and their catabolic markers, thrombospondin-5 (ADAMTS-5) and MMP-13, were also significantly reduced in the entire chondrocyte layer. Compared to a single injection, multiple HUC-MSCs injections better alleviated MIA induced infiltration of inflammatory cells on CD4+Th cells and CD68+macrophages, as well as synovial hyperplasia [7]. When combined with 4% sodium hyaluronate (HA), HUC-MSCs will proliferate faster and efficiently differentiate into chondrocytes (Fig. 2). In the pig OA model, transplantation of HUC-MSCs containing 4% HA not only improved macroscopic and microscopic histology, but also promoted the formation of cartilage in the treated joint [7]. When cultured in a bioreactor, the proliferation rate of HUC-MSCs is more than a thousand times that of bone marrow stem cells [9] (Fig. 2).

Mechanism of HUC-MSCs differentiated cartilage cells

The differentiation direction of HUC-MSCs is influenced by various conditions. The morphology of chondrocytes co-cultured with HUC-MSCs transfected with TDP43 Lentivirus changed significantly. The cell morphology becomes coarse, promoting chondrocyte proliferation and inhibiting cell apoptosis. After chondrocytes were co-cultured with TDP43 Lentivirus transfected HUC-MSCs, the expression of RACK1, JNK, AP-1, and Bcl xl genes was higher than that of chondrocytes co-cultured with non-transfected HUC-MSCs and vector Lentivirus transfected HUC-MSCs. High expression of TDP43 can activate the expression of RACK1, thereby regulating chondrocyte proliferation and apoptosis [10]. Compared with HUC-MSCs transfected with empty body Lentivirus, the morphology of chondrocytes co-cultured

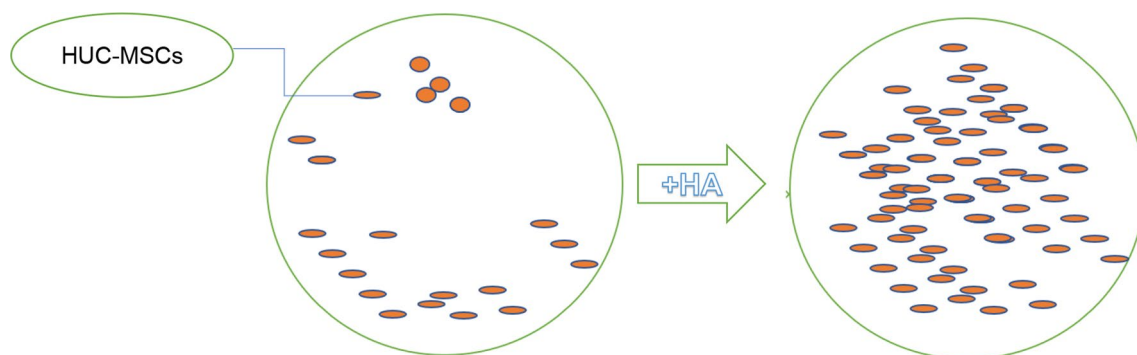


Fig. 2 HA promotes the generating of HUC-MSCs

with untransfected HUC-MSCs did not change, and they were spindle shaped adherent growth. The same research results indicate that HUC-MSCs stimulate local endogenous chondrogenitor cell differentiation through TSP-2, ultimately leading to cartilage regeneration [11]. Extracellular matrix (ECM) derived from cartilage can promote the transformation of HUC-MSCs into chondrocytes and promote cartilage formation. However, the role of HUC-MSCs stimulated by ECM in OA is still unclear. Cartilage acellular matrix (CAM) is a cartilage-derived ECM used to promote chondrogenesis in HUC-MSCs. Analyze the ability of HUC-MSCs to differentiate into cartilage using chondrogenic markers (aggrecan, type II collagen, and SOX9) and bone morphogenic protein 6 (BMP6). CAM treatment significantly increased the expression of chondrogenic markers and BMP6 in HUC-MSCs. In addition, HUC-MSCs and CAM treatment not only enhanced the synthesis of proteoglycans and Col2, but also enhanced the anti-inflammatory effects of rabbit joints and synovial fluid in the rabbit cruciate ligament transection (ACLT) model. The involvement of HUC-MSCs and BMP6 was also detected in rabbit cartilage tissue. Therefore, BMP6 can induce HUC-MSCs to generate CAM [12]. The combination of various biomaterials and HUC-MSCs is gradually being used to

treat OA. HUC-MSCs loaded with graphene oxide (GO) particles lubricant can promote the secretion of chondrocytes in OA animal models, reduce the level of intra-articular inflammation [13], improve subchondral bone osteoporosis, and promote cartilage repair [14]. The electrospun polycaprolactone (PCL) nanofiber network combined with HUC-MSCs for cartilage tissue engineering may also have an impact on OA. Compared with HUC-MSCs cultured on electrospun nanofiber net, articular chondrocytes isolated from human osteoarthritis joints have higher production of glycosaminoglycan and higher expression of cartilage related genes in HUC-MSCs cultured on basic medium. In addition, the presence of sulfated proteoglycans and ColIII was observed on both types of cell cultures. This effect is due to the structure of PCL or the inherent cartilage differentiation potential of HUC-MSCs [15]. In vitro research results indicate that platelet lysates (PL) significantly promote the proliferation of HUC-MSCs by upregulating related genes/proteins and activating Beclin1-dependent autophagy through the AMPK/mTOR signaling pathway. In vivo data indicate that the combination of PL and HUC-MSCs has a significant synergistic effect on OA. Overall, the beneficial effects and mechanisms of PL on HUC-MSCs were identified, and PL was indicated as an adjuvant for

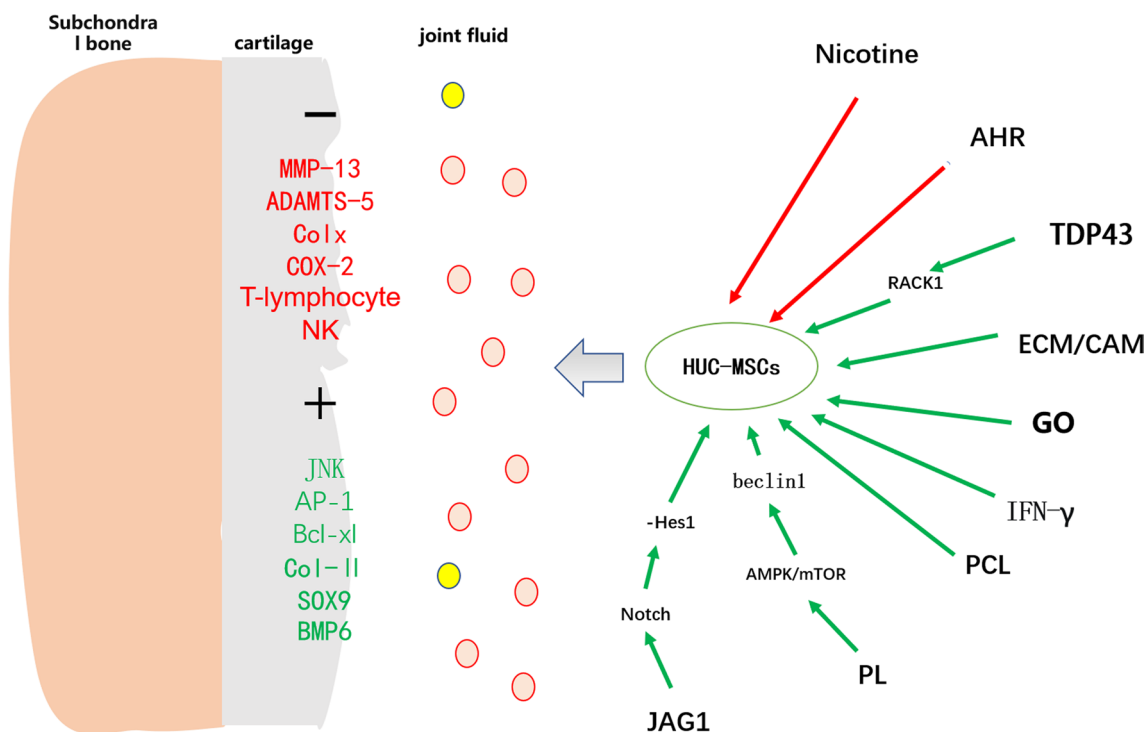


Fig. 3 Red: inhibition, Green: promotion

HUC-MSCs in treating OA [16]. The combination of soluble Jagged1 (JAG1) peptide and HUC-MSCs enhances the survival rate and cartilage differentiation of HUC-MSCs, reduces local inflammation, and further promotes its therapeutic effect. The inhibition of Notch targeting Hes1 expression by JAG1 can enhance the survival and cartilage differentiation of HUC-MSCs, thereby enhancing their therapeutic potential for cartilage regeneration [17]. In the study of UCB MSCs combined with 4% HA hydrogel composite on articular cartilage, the finding that transplanted cells disappear at the defect site shows that the paracrine interaction between UCB MSCs and host cells plays an important role in cartilage repair. UCB MSCs and 4% HA hydrogel composite may be a new treatment for full-thickness cartilage defects [18] (Fig. 3).

Inhibits the ability of HUC-MSCs to differentiate cartilage

Some substances inhibit the ability of HUC-MSCs to differentiate cartilage. In an OA patient and animal experiment, the synovial fluid of OA patients activated aromatic hydrocarbon receptor (AHR) expression in HUC-MSCs and inhibited cartilage differentiation. Inhibition of AHR expression relieves this inhibition [19]. Similarly, studies looking at the effect of nicotine on HUC-MSCs found that from the 3rd day of treatment, nicotine significantly impaired the proliferation of HUC-MSCs, but nicotine did not change the viability of HUC-MSCs, but the content of proteoglycans in the control group was richer than in the nicotine group, but there was no difference in total collagen content. The mRNA expression of SOX9, ColII, and aggrecan glycans in the control group was higher than that in the nicotine group. Calcium channels are initiated by $\alpha 7$ nicotinic acetylcholine receptor ($\alpha 7$ nAChR) after nicotine leads to calcium (Ca^{2+}) influx into HUC-MSCs to affect proliferation, so nicotine has adverse effects on the proliferation of HUC-MSCs and cartilage differentiation, which may be impaired by $\alpha 7$ nAChR mediation [20]. In vitro studies have shown that after stimulation by pro-inflammatory factors (IFN- γ), HUC-MSCs consume tryptophan through the kynurenine pathway by upregulating the mRNA of the immunomodulatory molecule indoleamine 2,3-dioxygenase (IDO), inhibit the proliferation of pro-inflammatory factors such as T cells and NK cells, and inhibit the inflammatory response [21].

HUC-MSCs-EV for knee osteoarthritis

EV inhibits OA inflammatory factors

Exosomes (EVs) are nanoscale membrane vesicles such as lipids, microRNAs, lncRNAs, and specific proteins between 40 and 100 nm [22]. HUC-MSCs-EV are produced by the endomorphous body network and pass through many different pathways such as the ESCRT

pathway acting on exosomal substances [23], inhibiting inflammatory mediators and MMP activity and promoting chondroprotective effects of anti-inflammatory cytokines on OA. It has become an excellent choice for the use of cell-free therapy in degenerative diseases through immunomodulation and tissue regeneration [24]. EVs have immunomodulatory and anti-inflammatory effects in various inflammatory diseases and tissue damage [25]. Most of the anti-inflammatory factors TSG-6 and IL-1RA in OA rats are derived from chondrocytes, and HUC-MSCs affect the OA microenvironment through EV and regulate inflammatory response [26]. When HUC-MSCs were injected intra-articularly, an increase in the expression of TNF- α -stimulated gene/protein 6 (TSG-6) in articular cartilage was observed and a decrease in MMP and ADAMTS-5 was observed. In addition, the expression of anti-calcitonin gene-related peptides in OA rats was also significantly reduced, indicating that it had an inhibitory effect on the central sensitizing component of pain [27]. There are many types of EVs. It has been found that the disappearance of transplanted cells at the defect site by intra-articular injection of UCB-MSCs overexpressing miR-140-5p combined with 4% HA hydrogel composite showed that EV can promote the expression levels of ColIII, aggrecan and SOX9 and inhibit the expression levels of mRNA and protein of NLRP3, caspase-1, MMP-13, and ADAMTS-5, inhibits cartilage degeneration in osteoarthritis rats, and improves cartilage repair function [28]. By miR-1208 targeting combined with METTL3 (METTL3 can play a protective role against OA), the m6A level of NLRP3 mRNA was reduced, the expression of ColIII and aggrecan was increased, the overexpression of ADAMTS-5 and MMP-13 in the knee joint of mice was inhibited, the secretion of pro-inflammatory factors was reduced, the progression of OA was slowed down, osteophyte production was reduced, the degradation of cartilage ECM was reduced, and the OA progression of mice was alleviated [29]. In vitro cell line analysis showed that EVs enhanced chondrocytes proliferation and migration while inhibiting apoptosis. HUC-MSCs produce nutritional effects on endogenous cell populations by secreting a large number of growth factors and cytokines, as well as immunomodulatory and anti-inflammatory molecules, EVs, etc.

EV acts on the signaling pathway of OA cartilage

Intra-articular injections of HUC-MSCs-EV can mitigate cartilage destruction and matrix degradation. EV maintains the chondrocytes phenotype by increasing ColII, synthesis and decreasing ADAMTS-5 expression through IL-1 β . Later, in animal experiments, it was shown that intra-articular injection of HUC-MSCs-EV successfully prevented cartilage destruction in DMM

models [30]. Intraperitoneal injections into OA animal models in HUC-MSCs-EV are made twice, one month after treatment. The results showed that EV is an effective treatment for reducing chemokines and cytokines in the serum of OA animals and aging-related secretory phenotyping (SASP). EVs are statistically significant compared to HUC-MSCs alone. Derived EVs show higher therapeutic potential. Systemic inflammation is improved by inactivation of the ERK1/2-AKT pathway in the in vivo OA model. EV treatment with mesenchymal stem cells previously modified to contain miR-21 antagonists is more effective at reducing systemic inflammation in age-related diseases than miR-21 in binding HUC-MSCs themselves. In addition, MSC-miR-21-derived EVs can modulate the ERK1/2 family to exert anti-inflammatory effects in the OA model via SDC1 [31].

Most EVs have limited access resources and are at risk of host rejection and immune response. The EVs of HUC-MSCs have the advantages of easy availability, minimal immune rejection, and good immunomodulatory effect. Although the exact mode of action of EV treatment for OA is unknown, there are various types of EVs, and the effect of different EVs on OA cartilage is also very different, and compared with normal cartilage, treatment with exosome MSC-92a-3p-Exos promotes HUC-MSCs cartilage proliferation and stromal gene expression. Conversely, treatment with MSC-anti-miR-92a-3p-Exos inhibits cartilage differentiation and reduces cartilage matrix synthesis by enhancing the expression of WNT5A. Further studies showed that miR-92a-3p inhibited the activity of reporter gene constructs containing 3'-untranslated regions (3'-UTR) and inhibited the expression of WNT5A, regulating cartilage development and homeostasis. Exosome miR-92a-3p may act as a Wnt inhibitor and have shown potential as a disease-modifying osteoarthritis drug [32].

In animal studies, EVs at 15 µg/mL showed maximum proliferation and migration capacity. This effect is caused by maintaining cartilage homeostasis, as evidenced by an increase in COLII and a decrease in MMP-13 and ADAMTS-5. M1 macrophage markers (CD14) were significantly reduced for HUC-MSCs and HUC-MSC-EV, while M2 macrophage markers (CD206 and IL-10) were increased. Cartilage repair-related proteins are more abundant in EVs. Compared with HUC-MSCs, upregulated proteins in EVs are mainly involved in the regulation of immune effector processes, extracellular matrix tissue, PI3K-AKT signaling pathway, and Rap1 signaling pathway. However, the disadvantages of EV treatment, such as the additional pain caused by multiple injections, the high cost of isolation methods, and the low enrichment of EVs, require further research [33].

Clinical application of HUC-MSCs in the treatment of OA

Essay	Sample size (example)	Observe the metrics	Duration of follow-up (yea)	Injection dose (pcs/ml)	Results
Günay [34]	10	VAS, WOMAC, and Lequesne scored 36 short health surveys. On MRI imaging, tumor necrosis factor α , interleukin-1 β , adiponectin, resistin, and interleukin-6	1 year	1×10^8 /1 ml	VAS, WOMAC, and Lequesne scores were lower, with 36 short health surveys having higher average scores. On magnetic resonance imaging, it was found that the thickness of cartilage was increased. Tumor necrosis factor α , interleukin-1 β , adiponectin, resistin, and interleukin-6 levels were significantly elevated
Suh [35]	43	Patients with HTO with ICRS class IV and medial femoral condyle cartilage defects greater than 200 mm ² were included. Clinical, Hospital for Special Surgery (HSS), International Knee Literature Committee (IKDC), and Lysholm scores were assessed 18 months postoperatively	1.5 years	7.5×10^6 /1.5 ml	The clinical efficacy and JSW of HUC-MSCs in HTO patients were better than those of microfractures
Lim [36]	144	International Knee Documentation Committee (IKDC) and Lysholm score	5 years	7.5×10^6 /1.5 ml	In older patients with symptomatic, large, full-thickness cartilage defects with or without osteoarthritis, HUC-MSCs-HA implantation improves cartilage grade at arthroscopy and improves pain and function over 5 years compared with microfractures

Essay	Sample size (example)	Observe the metrics	Duration of follow-up (yea)	Injection dose (pcs/ml)	Results	Essay	Sample size (example)	Observe the metrics	Duration of follow-up (yea)	Injection dose (pcs/ml)	Results
Song [37]	125	Imaging, mechanical axes, and JSW	3 years	$7.5 \times 10^6/1.5$ ml	HUC-MSCs in combination with HTO is an effective treatment for patients with medial ventricular osteoarthritis and varus deformity.	Yang [43]	28	WOMAC, VAS SCORE, SF-13, OVERALL PATIENT ASSESSMENT, AND RHEUMATOLOGY COMMITTEE (OMERACT) OARSI, WOMAC, KNEE MRI EVALUATION AND BLIND ASSESSMENT	1 year	1.5×10^7 /ml	The effect begins 1 month after injection, and the therapeutic effect can last for 6 months
Song [38]	25	ICRS, histological assessment; VAS score, WOMAC, KDC score	1–2 years	$7.5 \times 10^6/1.5$ ml	ICRS raised by 1 level. In patients over 60 years of age with OA, HUC-MSCs implantation achieves satisfactory cartilage regeneration and shows satisfactory clinical results	Chung [44]	93	Safety, VAS score, International Knee Documentation Committee (IKDC) subjective score, MRI, histological evaluation	1.7 years	0.5×10^7 /ml	HUC-MSCs knee injections can treat severe OA
Dilogo [39]	29	Age > 40 years, 0.4 year varus deformity > 5°, (ICRS) grade IV articular cartilage damage > 4 cm ²	0.4 year	$1 \times 10^7/2$ ml	HUC-MSCs achieve maximum effect after 6 months of injection	Samara [1]	16	Clinical treatment was evaluated using SF-36 scale, Lysholm score, and WOMAC score	2 years	0.6×10^6 /ml	Sodium hyaluronate provides faster, more significant, and longer-lasting relief
Matas [40]	18	IKDC score, VAS, WOMAC score	1 year	$2 \times 10^7/3$ ml	In phase I/II clinical trials, repeated HUC-MSCs injection strategies resulted in good safety and improved clinical outcomes for treating long-term pain in patients with knee OA						
Park [41]	9	MRI, arthroscopy to assess cartilage regeneration	7 years	0.5×10^7 /ml	Histology after 1 year shows hyaline cartilage. MRI after 3 years showed that the regenerative cartilage persisted. No bone changes were found within 7 years						
Wang [42]	18	Kellgren–Lawrence Level I–IV examination. MRI findings	0.5 year	$(2–3) \times 10^7$ /mL	Intra-articular injections of HUC-MSCs for OA significantly improve joint function and quality of life						

HUC-MSCs have long-term effects in patients with OA

With the remarkable results of HUC-MSCs in the treatment of OA in basic trials, HUC-MSCs have gradually begun to be studied in clinical practice. Most of the HUC-MSCs used in clinical practice are allogeneic stem cells derived from umbilical cord blood with sufficient growth factors and cytokines for regeneration. Clinical studies of high tibial osteotomy (HTO) versus HUC-MSCs have reported good clinical outcomes and cartilage regeneration, producing more hyaline cartilage than microfractures (MFx) in patients over 50 years of age. The current study is consistent with these results and has good clinical outcomes and an increase in joint space (JSW) in elderly patients. In a multicenter randomized study of HUC-MSCs and MFx, HUC-MSCs showed better cartilage regeneration in clinical outcomes 48 weeks postoperatively. However, after HUC-MSCs treatment, clinical outcomes are better 3–5 years after surgery in patients with OA. HUC-MSCs can enhance cartilage regeneration in HTO patients with cartilage defects greater than 200mm² [35]. At 48 weeks, the International Society for

Cartilage Repair (ICRS) grade improvement was 1 grade higher in the umbilical cord-derived mesenchymal stem cells combined with 4% hyaluronic acid (HUC-MSCs-HA) compared with the microfracture group; the overall histological assessment score of the HUC-MSC-HA group was also better than that of the MFx group. Clinical outcomes in the HUC-MSCs-HA group improved significantly at 3- to 5-year follow-up. Studies have also shown the greatest improvement in knee function after 6 months of follow-up [39]. This new application of HUC-MSCs-HA may be applicable to OA patients. HUC-MSCs-HA may be an alternative to single-compartment knee replacement for patients who wish to preserve the joint and maintain an active lifestyle. In patients with OA more than 7 years after treatment, improved clinical outcomes did not deteriorate significantly. Cartilage repair by HUC-MSCs-HA can lead to sustained clinical improvement within 5 years of intervention, which is highly beneficial for joint protection. Large full-thickness cartilage defects can also be regenerated for treatment [36]. The clinical impact of HUC-MSCs treatment exceeds the expected placebo effect described by most treatments for knee osteoarthritis [45]. In phase I/II randomized, controlled, triple-blind trials of HUC-MSCs followed by 6 or 12 months follow-up, no changes were found, possibly due to a slight effect on imaging and a low initial WOMS score, although studies have shown the preventive effect of MSC cell therapy on OA development, so long-term 2-year data were collected. The control group was found to have an increased chance of disease progression at 2 years of follow-up [40].

Factors influencing HUC-MSCs in the treatment of OA

The formation of OA is affected by many factors, obesity, age, work environment, and activity level which are all important factors affecting the clinical outcomes of OA patients. However, clinical observations in patients with OA treated with HUC-MSCs showed that clinical scores at 2 years after injection improved compared with 1 year, regardless of obesity. Age is an important factor influencing clinical outcomes. <65-year-old OA patients outperformed the ≥ 65 -year-old group in IKDC scores at 1 and 2 years and VAS at 2 years. And the younger the age, the higher the improvement in IKDC, VAS, and WOMAC scores in patients with OA. The ≥ 65 -year-old group will also improve over time. In addition, chondrogenic activity of HUC-MSCs is also reduced in cultures from patients with advanced OA [44]. The size of the cartilage defect is also another factor affecting clinical outcomes, but is not associated with 1- and 2-year IKDC, VAS, and WOMAC scores [38]. The number of stem cells regarding defective size has not been standardized, and further investigation is needed, because the results of another

study showed that the advanced age or older cartilage damage in patients had no significant effect on the clinical outcome of HTO and implantation of HU-CMSCs in OA patients [37]. However, local injection of HUC-MSCs in the treatment of degenerative knee osteoarthritis had a significantly better duration of efficacy after treatment than local injection of sodium hyaluronate [42].

Safety analysis of HUC-MSCs in the treatment of OA

HUC-MSCs treated with OA patients had fewer adverse effects, and no significant differences in overall or treatment-specific adverse events were observed between the HUC-MSCs group and the microfracture group in the initial 48-week clinical trial and 60-month follow-up survey. Nor did participants drop out of the study due to adverse events. Three serious adverse events (SAEs) occurred in 3 participants treated with HUC-MSCs in combination with HA, compared with 1 participant in the microfracture group with 2 SAEs in the first 48 weeks. Pain at the treatment site in the HUC-MSCs-HA group is thought by the investigators to be related to the treatment modality. At 60 months of follow-up, 8 SAEs occurred in 7 participants in the HUC-MSCs-HA group and 7 in 5 participants in the microfracture group. The researchers believe that none of the SAEs were associated with treatment. Among them, OA patients who underwent total knee replacement and high tibial osteotomy were considered to have a natural history of osteoarthritis, rather than implantation of the HUC-MSCs-HA complex. One death due to myocardial infarction (41 months after intervention) was reported in the HUC-MSCs-HA group. In an additional [45], participants treated with HUC-MSCs-HA, no immune response was observed. Also in other studies, in clinical trials of seven patients with Kellgren–Lawrence class III osteoarthritis and ICRS class IV cartilage defects [46]. Five participants reported mild to moderate adverse events, but no serious adverse events such as arthralgia, back pain, bladder dilation, and elevated levels of anti-thyroglobulin antibodies. Only those classified as “increased susceptibility to infection” according to WHO criteria were identified as treatment emergency adverse events (TEAEs). An internal medicine specialist judged that it did not require additional treatment and returned to normal automatically. Prospective follow-up was conducted for at least one year in patients who received HTO therapy and HU-CMSCs implantation with full-thickness cartilage injury in the knee with osteoarthritis. Ninety-three patients were followed for an average of 1.7 years (range 1.0–3.5 years). The average size of cartilage lesions was 6.5 cm^2 (range $2.0\text{--}12.8 \text{ cm}^2$). After HUC-MSC implantation, no persistent effusion, synovitis, local rash, or local erythema were found. Some patients have knee swelling

for up to 1 month after surgery and require pain medication [43]. At 7-year follow-up, no specific adverse effects were observed in 6 participants. During follow-up, no participants underwent additional knee surgery or knee replacement due to knee pain, exacerbation, or impaired function. Only one participant died during the long-term extension period because she died of frail old age 6 years after transplantation at the age of 76. Nor were any unusual findings indicating rejection or infection. None of the participants had substantial permanent morbidity, and none of the participants terminated the study prematurely after transplantation. Although they use allogeneics, HUC-MSCs result in less rejection due to their low immunogenicity and immunomodulatory activity. Another notable finding was that the improvement in pain and function 24 weeks after transplantation did not deteriorate significantly within 7 years. Participants in the study were patients with K-L III OA but did not undergo any additional knee surgery or knee replacement surgery during the 7-year follow-up period after transplantation [41]. Similarly, a meta-analysis evaluating the safety of HUC-MSCs over 15 years found that HUC-MSCs administration was significantly associated with transient fever, adverse events at the site of administration, constipation, fatigue, and insomnia. Despite these barriers, there is evidence that HUC-MSCs injections have a beneficial effect in the treatment of knee osteoarthritis [47].

In a randomized semi-blind experiment, the symptoms and signs of self-perceived abnormalities occurred in the trial, mainly including increased blood pressure, dizziness, insomnia, hot flashes, epigastric discomfort, nausea, transient joint pain aggravation (≤ 24 h), influenza symptoms, etc. Among them, 2 cases (13.3%) occurred in the 2 injections of HUC-MSCs (15 cases), of which 1 case was mildly untreated and self-healed, and 1 case had moderate increase in blood pressure (150/100 mmHg) and was treated symptomatically to improve with anti-hypertensive treatment. A total of 3 adverse events occurred in 4 injections of HUC-MSCs (13 cases) (incidence 21.4%), all of which were mild untreated self-healing. There were no significant differences in the incidence of adverse events between 2 and 4 injections and the incidence of individual adverse events. Laboratory tests showed 2 injections of HUC-MSCs with abnormal liver function (mild elevation of ALT/AST) in 2 cases (incidence 13.3%), which were mildly elevated and normal without treatment. Liver dysfunction (mildly elevated ALT/AST) in 4 injections of HUC-MSCs was mild in 1 case (incidence 13.3%), and untreated re-examination was normal [43]. Treatment was well tolerated. Function and pain improved significantly at 12 and 48 months, MRI scans showed statistically significant improvements in cartilage loss, osteophytes, bone marrow lesions,

effusions, and synovitis at 12 months, and subchondral sclerosis was very significant.

In addition, a total of 29 *in vivo* studies were identified and analyzed in the PubMed and Scopus databases. Studies reported outcomes in EV delivery and uptake *in vivo*; improve cartilage morphology, histology, and biochemical outcomes; enhance subchondral bone regeneration; and improvement of painful behavior after EV treatment. Studies have demonstrated that EV treatment is safe, as no significant complications were found in all included studies. EV administration is an effective cell-free therapy for the relief of OA. However, further research is needed to confirm the therapeutic potential of EVs and to determine the standard regimen for OA based on EV therapy.

Discussion

The onset of OA patients is affected by a variety of factors, which eventually lead to the loss of cartilage in the joints, the formation of osteophytes, the loss of normal knee mobility, and pain and discomfort, which seriously affects the quality of life. Articular cartilage is mainly composed of chondrocytes and extracellular matrix, because cartilage does not contain blood vessels and nervous system, and the required nutrients depend on the synovial fluid of the joint and the arterial layer branches around the synovial membrane to maintain the normal synthesis and metabolism of chondrocytes. Articular cartilage exists at the junction of adjacent bones, its surface is smooth and elastic, can play a buffer role when the joint moves, and is indispensable for maintaining the normal function of the joint, but this also makes the joint cartilage extremely vulnerable to destruction. Therefore, preventing the loss of articular cartilage is essential to prevent the development and development of OA.

HUC-MSCs are a relatively novel source of mesenchymal stem cells for the treatment of OA. HUC-MSCs extracted from the umbilical cord have a greater proliferative capacity and are not subject to the same ethical controversy as human embryonic stem cells. Mesenchymal stem cells derived from the umbilical cord offer multiple advantages in osteoarthritis cartilage repair over other sources of mesenchymal stem cells. First, newborn umbilical cord specimens are abundant and can be provided in large quantities. Second, there is no trauma or pain to the individual during the collection process. Third, proliferation is rapid and non-tumorigenic. Fourth, as a pluripotent stem cell, due to its multi-directional differentiation potential, it can differentiate into a variety of cells under certain conditions, participate in the repair of tissue damage, and have higher inducibility. Fifth, a large number of cytokines can also be secreted through paracrine function to participate in the inflammatory immune regulation process, making HUC-MSCs

ideal cells for the treatment of OA cartilage damage. And compared with bone marrow mesenchymal stem cells, UHC-MSCs show significantly higher chondrogenesis potential and relatively lower osteogenic and lipogenic capacity. In the process of cartilage formation, the expression of cell proliferation, adhesion molecules, signaling molecules, and chondrogenesis-specific genes of UHC-MSCs is significantly increased. For therapeutic effect, in arthritis models, UHC-MSCs can increase the synthesis of ColIII and reduce proteoglycan expression of pro-inflammatory cytokines. And HUC-MSCs contain a large number of growth factors, cytokines, hyaluronic acid, and extracellular vesicles [47]. Through cytokine profiling, IL-10, ICAM-1, and TGF β 1 were also upregulated more pronounced in UHC-MSCs. UHC-MSCs do have a particular advantage over bone marrow mesenchymal stem cells in terms of cartilage regeneration [48]. Under anaerobic conditions, undifferentiated HUC-MSCs can produce better extracellular matrix (ECM). Compared to bone marrow mesenchymal stem cells, HUC-MSCs produce higher amounts of type II collagen, specifically the IIB subtype, and also produce type I collagen and Htra1 collagen [49]. The biological advantages of HUC-MSCs include high proliferation rate and clonality, anti-aging, and excellent anti-inflammatory effects. In recent years, drugs mixed with HUC-MSCs with hyaluronic acid have been widely used in clinical settings. HUC-MSCs have the advantage of low immunogenicity, and the cartilage formed can display a hyal-like histological morphology [50]. HUC-MSCs can also inhibit the expression of calcinogen 11 (CDH11) in rheumatoid arthritis (RA) via fibroblast-like synovial cells (FLS). This mechanism may help improve arthritis [51].

The number of injections used in the treatment has also not been clearly defined in the current study, and in the ACLT-induced rat model, single versus two injections of 1 ml at a concentration of 1×10^6 (cells/ml) were compared and followed for 12 weeks. Serial sections of the knee were subjected to histological, immunohistochemical, and TUNEL analysis. Results: Transplantation of HUC-MSCs significantly reduced the development of OA-induced by ACLT surgery. Significantly promotes ACLT-induced synthesis of chondrocytes extracellular matrix synthesis (aggrecan). TUNEL analysis showed that HUC-MSCs treatment significantly protected chondrocytes from apoptosis. No significant differences were observed between single and repeated injections. In vitro HUC-MSCs show good cartilage-forming potential, although HUC-MSCs exhibit excellent proliferative capacity. However, single or two injections of HUC-MSCs significantly inhibited the progression of ACLT-induced OA rats with similar effects, and HUC-MSCs

reduced ACLT-induced apoptosis of arthritic chondrocytes [52]. Similarly, HUC-MSCs transplantation for severe OA can reduce joint pain and improve joint function more quickly, significantly and durably than sodium hyaluronate, and the efficacy of 4 injections is better than 2 injections. Therefore, multiple injections may produce better results.

HUC-MSCs are well tolerated, effective, and safe in the treatment of patients with OA. Repeated dosing and higher concentrations led to better clinical improvement. A reduction in cartilage loss was observed in some HUC-MSCs trials. No serious adverse effects were recorded. Treatment in KOA-KL II-III may be more effective [53]. In a non-randomized, open-label, multicenter trial, Ashim Gupta et al. came to the same conclusion [54].

Conclusion

HUC-MSCs can reduce inflammatory factors such as MMP-13, ADAMTS-5, IL-1 β , IL-1, IL-1, IL-6, TNF- α , M1 polarization in OA and protect cartilage damage. At the same time, the synthesis of ColII, SOX9, aggrecan, etc., promotes cartilage synthesis, promotes cartilage synthesis through P13/Akt, mTOR, Notch, and other cell signaling pathways, and acts on THP-1 to induce the conversion of M1 to M2 to reduce the level of OA inflammation. Clinically, HUC-MSCs produce more hyaloid cartilage than MFx in patients older than 50 years of age. Better cartilage regeneration was shown in clinical outcomes 48 weeks postoperatively. These studies also suggest that HUC-MSCs can enhance cartilage regeneration in HTO patients with cartilage defects greater than 200mm², and that treatment in KOA-KL II-III may be more effective than sodium hyaluronate for the treatment of severe cartilage damage. In terms of safety, it is mainly pain-based and can recover on its own, without intervention and treatment, which is relatively safe.

Further study

There are many factors in the treatment of OA by HUC-MSCs, such as the extraction, storage, temperature, and use of preservatives or catalysts for HUC-MSCs, which can affect the effectiveness of treatment. There is also no clear definition of the dose of OA treatment, and 7.5×10^6 cells/1.5 ml are used in existing articles, and the safety profile is better. Therefore, we are far from knowing the optimal conditions for using HUC-MSCs as a therapeutic tool in preclinical and clinical trials of OA. Although many clinical, radiographic, and histological studies have shown that HUC-MSCs improve knee chondrocytes. More basic research and multicentre randomised clinical studies are needed to determine the significant clinical impact on OA.

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Author contributions

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Availability of data and materials

This study collected CNKI, Wanfang, PubMed, and articles related to the treatment of OA with HUC-MSCs since their publication, excluding non-basic and clinical studies such as reviews and meta-analysis. A total of 31 basic experimental studies and 12 clinical studies were included. Systematically analyze the effects of HUC-MSCs on inhibiting inflammatory factors, promoting chondrocyte production, and current clinical treatment.

Declarations

Ethics approval and consent to participate

Not applicable.

Competing interests

The author declare that they have no competing interests.

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