International Journal of Research in Orthopaedics
Suárez KM et al. Int J Res Orthop. 2024 May;10(3):647-654
http://www.ijoro.org

DOI: https://dx.doi.org/10.18203/issn.2455-4510.IntJResOrthop20240935

Systematic Review

Advances in stem cell therapy for articular cartilage lesions: clinical evidence and future directions: a systematic review

Kevin Miranda Suárez[1]*, Claudia Anabel Pesantez Zea[2], Mateo Daniel Fabara Vera[3], Bryan Steven Pasquel Rodríguez[3], Andrea Janet Zambrano Garces[4], Erick Santiago Velastegui Jijón[5], Angel Eduardo Romo Quintana[6], Katherine Lizeth Bautista Suárez[7]

[1]Department of Orthopedics, NOVA Clínica Santa Cecilia, Ecuador
[2]Department of Medicine, Universidad Catolica Azogues, Ecuador
[3]Department of Medicine, Universidad De Las Américas, Ecuador
[4]Department of Medicine, Universidad De Guayaquil, Ecuador
[5]Department of Aesthetic Medicine, Nutrition and Anti-aging, Distance University of Madrid (UDIMA), Spain
[6]Department of Medicine, Universidad Central, Ecuador
[7]Department of Medicine, Ministerio De Salud Pública, Ecuador

Received: 11 March 2024
Revised: 01 April 2024
Accepted: 04 April 2024

***Correspondence:**
Dr. Kevin Miranda Suárez,
E-mail: srammswish@hotmail.com

ABSTRACT

The significance of articular cartilage, an essential connective tissue, cannot be overstated in relation to joint health and functionality. Nevertheless, the human body might have adverse effects due to traumatic incidents, degenerative conditions, or repetitive stress, resulting in the manifestation of pain, inflammation, and impaired functionality. The primary objective of this study is to assess the effectiveness of stem cell therapy in the treatment of articular cartilage damage such as lesions. The systematic review was conducted adhering to the PRISMA principles. Boolean logic is employed in the search technique to integrate phrases pertaining to stem cell therapy, articular cartilage diseases, and biological processes. The research employs a range of databases and medical subject headings (MeSH) in order to facilitate a thorough examination. The stem cell therapy in the treatment of articular cartilage lesions has great potential. It enhances management and treatment outcomes for individuals afflicted with cartilage abnormalities. It is beneficial particularly those diagnosed with osteoarthritis (OA). Encouraging outcomes, such as alleviation of pain and improvement in functionality have been reported. Additional investigation is required to enhance therapy regimens, encompassing cell dosage, delivery techniques, and supplementary medicines. The use of stem cell therapies necessitates the imperative collaboration among researchers, doctors and regulatory agencies.

Keywords: Stem cell therapy, Articular cartilage lesions, Cartilage

INTRODUCTION

Articular cartilage is a form of connective tissue that surrounds the extremities of bones. The cartilage serves a vital role in maintaining joint health and functionality through several mechanisms. These include the provision of a smooth surface, effective shock absorption, even distribution of load and production of synovial fluid.[1] The supply of nutrients via avascular pathways are also included. The composition of articular cartilage consists of

water, collagen fibres, and proteoglycans, which contribute to its durability, flexibility, and resilience. The health and integrity of the joint are crucial for its proper functioning and ability to move. It is crucial to uphold joint health and mobility by ensuring preservation of articular cartilage health.[2] Pain, inflammation, and loss of joint function can result from damage or degeneration or lesions.

Articular cartilage lesions refer to abnormalities in the smooth cartilage that covers the ends of bones in joints. These problems may arise as a result of traumatic events, degenerative disorders such as OA, or repetitive stress.[3] Typical symptoms are arthralgia, edoema, rigidity, and diminished functionality. Untreated lesions can deteriorate and lead to the development of disorders such as OA. The choice of treatment is dependent upon various parameters, including the size, severity, age, activity level, and joint location of the patient.[4]

The healing potential of articular cartilage is significantly constrained due to its limited regeneration capacity and lack of blood vessels. The complete restoration of articular cartilage's structure, function, and biomechanical qualities is improbable following damage. It typically signifies progression towards the development of OA.[5] Arterial cartilage abnormalities are frequently detected in individuals without any health conditions by the use of magnetic resonance imaging (MRI) assessment. The precise prevalence of cartilage lesions remains uncertain. The research indicates that articular abnormalities are observed in approximately 60% to 66% of knees that undergo arthroscopy.[6] Approximately 900,000 Americans are affected by cartilage injuries of the knee each year, leading to over 200,000 surgical treatments.[2,6]

Given the wide range of disease associated with articular cartilage injury, which includes single, focal chondral defects as well as progressive degenerative illnesses and end-stage OA, it is crucial to acknowledge that only a minority (approximately 5%) of defects are observed through MRI. Therefore, the task of identifying patients in need of cartilage repair poses a substantial barrier that necessitates meticulous evaluation of multiple parameters. Cartilage injury can result from different causes, such as sudden traumatic injuries, early degenerative changes after trauma and repeated microtrauma over time. Developmental problems like osteochondritis dissecans (OCD), or acquired metabolic variables like avascular necrosis can also act as contributory factors towards cartilage injury. The prevalence of patients reporting a traumatic versus gradual onset of symptoms, together with the presence of cartilage lesions in all three compartments of the knee, is about equal.[2]

Lesions are predominantly observed on the weight-bearing femoral condyle, accounting for around 43% to 58% of cases. It is observed with a higher concentration on the medial condyle. Patellar lesions include approximately 11% to 36% of the total number of lesions. Simultaneously, trochlear lesions are observed with a lower frequency, ranging from 6% to 16% of cases. The defect size is often smaller than 4 cm^2 in 90% of incidences. Engaging in sports activities is often linked to the identification of chondral lesions.[2]

Possible courses of action encompass conservative strategies such as rest, physical therapy, and pain management, with more intrusive therapies such as arthroscopic surgery or techniques for cartilage restoration. Prompt identification and treatment are essential for maintaining the structural soundness of joints and averting additional harm.[7]

Therapies for articular cartilage lesions are designed to help reduce symptoms, encourage healing, and restore joint function. There are different treatment options available depending on factors like the size, location, and severity of the lesion, as well as the patient's age, activity level, and overall health.[8]

When it comes to conservative management, it usually includes a mix of rest, making changes to your activities, undergoing physical therapy, and using strategies to manage pain like taking nonsteroidal anti-inflammatory drugs (NSAIDs) or getting corticosteroid injections. These approaches can potentially reduce inflammation, alleviate pain, and enhance joint mobility, all while enabling the body's own healing mechanisms to occur.[9]

If conservative measures don't work or if the condition is more severe, doctors may need to consider more invasive treatments. Arthroscopic surgery is a procedure that is minimally invasive, meaning it doesn't require large incisions. It can be used to directly assess and treat the lesion. Surgeons have various techniques at their disposal to help with healing. They can remove damaged tissue through a process called debridement. Another method involves creating small fractures in the bone to stimulate the growth of new cartilage, known as microfracture. Additionally, drilling can be used to encourage the formation of fibrocartilage.[10]

If the lesion is larger or more complex, we may use advanced cartilage repair techniques. Autologous chondrocyte implantation (ACI) is a procedure where doctors take healthy cartilage cells from the patient, grow them in a lab, and then put them back into the damaged area to help the cartilage grow back. MACI, which stands for matrix-induced autologous chondrocyte implantation, is a procedure that involves using a collagen scaffold to provide support for the implanted cells.[11]

Stem cell therapy is a really promising approach to repairing cartilage. One possible treatment option is to inject mesenchymal stem cells (MSCs) directly into the damaged area. These cells have the ability to transform into different types of cells, such as cartilage cells called chondrocytes. By doing this, the hope is to encourage the regeneration and repair of the tissue. Furthermore, a

treatment called platelet-rich plasma (PRP) therapy can be used to inject concentrated platelets from the patient's own blood into the joint. This therapy has the potential to promote healing and decrease inflammation.[12]

Typically, the therapy chosen for articular cartilage lesions is based on several factors, and treatment plans are usually tailored to meet the specific needs and circumstances of each patient. In order to effectively manage a patient's condition, it is important to take a multidisciplinary approach. This entails involving orthopaedic surgeons, physical therapists, and other healthcare professionals. By doing so, we can optimise outcomes and ensure the preservation of joint health and function.[13]

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This study aims to comprehensively evaluate clinical evidence for advancing stem cell therapy in treating articular cartilage lesions and outline future directions for treatment of articular cartilage lesions

METHODS

Data sources and search strategy

The importance of choosing the right research methods to study the effectiveness of stem cell therapy for articular cartilage injuries is emphasised. This research follows the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines to make sure that relevant studies are thoroughly and systematically explored. The search strategy uses Boolean logic to combine different terms related to stem cell therapy, articular cartilage lesions, and relevant biological processes. A thorough search across various databases was conducted such as Elsevier, Scopus, ResearchGate, the national library of Frontiers, PubMed central (PMC), PubMed/Medline, and Google Scholar. MeSH were used to improve the accuracy of my search. The search terms like "stem cell therapy," "articular cartilage lesions," "stem cells," and "chondrogenesis" were used. Keywords utilized for this research are listed in Table 1. This systematic approach ensures that all relevant factors are considered and allows for a comprehensive investigation into the effectiveness of stem cell therapy for treating articular cartilage lesions.

Table 1: Keywords and MeSH phrases utilized in the systematic review.

Category	Keywords/MeSH phrases
Articular cartilage	"Articular surface" or "cartilage" or "joint cartilage" or "hyaline cartilage" or "extracellular matrix"
Lesions	"Defects" or "injuries" or "abnormalities" or "pathologies"
Stem cell therapy	"Regenerative medicine" or " cell-based therapy" or "stem cell transplantation" or "cellular therapy" or "mesenchymal stem cells (MSCS)" or "adult stem cells" or "embryonic stem cells"
Future recommendations	"Prospective" or "effectiveness" or "development"
Clinical evidence	"Therapeutic efficacy" or "treatment outcomes" or "intervention effectiveness" or "evidence-based medicine" or "healthcare interventions"

Eligibility criteria and study selection

In order to investigate stem cell therapy for articular cartilage diseases, the eligibility criteria were established. For evaluation, conditions for inclusion and exclusion were developed. Articles that specifically focused on stem cell therapy for articular cartilage diseases were taken into consideration for inclusion in the literature. The research articles conducted in the last five years were included. For the purpose of guaranteeing scientific rigour and correctness, only research that were either published in English were included. The investigations subjected to peer review were considered for inclusion. A significant contribution to the selection process was made by the reviewers. Exclusion criteria were utilised in order to avoid works that did not provide a thorough overview of the subject matter or translations that were readily available. This was done in order to guarantee linguistic consistency and accessibility. The accuracy and precision of the research evaluation were improved as a result of adhering to these standards, which maintained the methodological integrity of the study.

Data collection and data items

The study on stem cell therapy for articular cartilage lesions followed a careful methodology that included a thorough selection process to maintain consistency and transparency. During the screening process, reviewers were given the responsibility of assessing research ideas based on predefined criteria in order to determine whether to approve or deny them. Following the PRISMA

guidelines closely, we analysed the paper titles and abstracts, and thoroughly reviewed the qualifying articles.[14] Figure 1 shows the PRISMA flow diagram that was used to identify research. We conducted careful selection and organisation of appropriate clinical trials to ensure reliability and precision. In addition, careful examination of each search result was conducted to improve reliability and reduce the chance of any bias in the selection process.

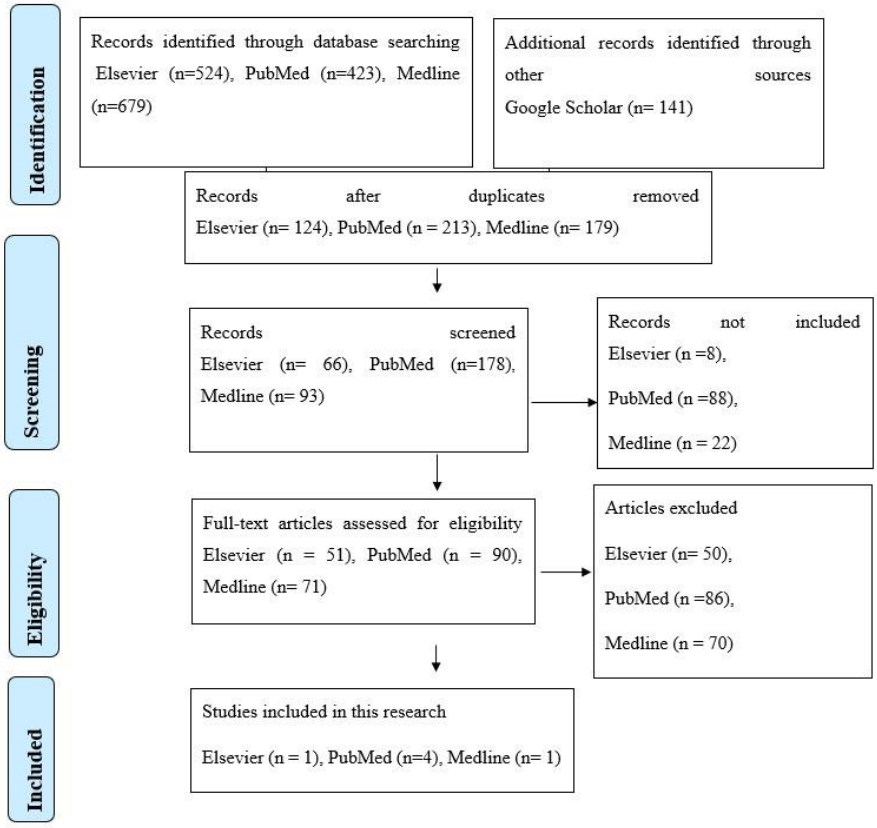

Figure 1: PRISMA diagram.

Data management

It is important to have effective data management in research studies so that the results can be reliable and accurate. The data is securely stored on a Google drive account. The researchers used their personal laptops to protect and store their research, publications, and results, ensuring the safety and privacy of the content. The researchers use their personal laptops for all operations, like downloading and analysing data. Furthermore, preservation and storage of data was done via cloud storage, USB devices, and CDs, which are widely used for data storage and management.[15]

A thorough search of all relevant databases turned up six articles that could be included in this systematic review. Figure 1. showed the selection process in more detail. It shows that 146 articles were first pulled from databases, and 23 articles from other sources were added. After getting rid of duplicates based on title, authors, and abstract, there were still 98 papers left. Out of these, 76 duplicates and papers that didn't explain their methods clearly or give correct data were thrown out. After that, 42 factors for eligibility were used, and 33 articles were chosen to be reviewed and evaluated. Particularly, 33 publications were thrown out for a variety of reasons, such as using unclear analysis methods or data that was more than five years old.

Study period

The exact study period for this systematic review spanned from March 1st to March 25th 2024.

RESULTS

The study was conducted for a comparative analysis of the clinical, radiological, and second-look arthroscopic results associated with the single or combined use of MSCs and allogenic cartilage in individuals diagnosed with varus knee OA. A cohort of eighty individuals was randomly assigned to two distinct groups. One group was the MSC implantation group (MSC group) and the other group was the MSC implantation with allogenic cartilage group (MSC-AC group). The Lysholm score and the knee injury and OA outcome score (KOOS) were used to assess

clinical outcomes before the surgery and at each follow-up visit. The femorotibial angle and posterior tibial slope were used to assess radiological outcomes. The evaluation of cartilage regeneration after second-look arthroscopy was conducted based on the Kanamiya grade. The findings demonstrated notable enhancements in clinical outcomes during the second-look arthroscopy. It was followed by additional improvements during the final follow-up. The MSC-AC group had considerably higher Kanamiya grades compared to the MSC group. The study's findings indicate that the combination of MSCs and allogenic cartilage is more effective than using MSCs alone for cartilage regeneration, resulting in the improved clinical outcomes.[16]

Similarly, study conducted to assess the midterm outcomes, survival rates, and determinants influencing the survival rate of MSC implantation in the treatment of knee OA lesions. A retrospective analysis was performed on a cohort of 467 patients who received MSC implantation on a fibrin glue scaffold. The follow-up period was of 5 years. The clinical outcomes were assessed using the IKDC and Tegner activity scale, which were measured before the surgery and repeated during the follow-up period. The evaluation of standard radiographs was conducted utilising the Kellgren-Lawrence grading system. The researchers conducted statistical analysis in order to ascertain the survival rate. The examination of the impact of various factors on the clinical outcomes was also done. The findings indicated a considerable improvement in the mean IKDC scores and Tegner scores until the 3-year postoperative period. However, there was a steady reduction in these scores from the 3-year to the 9-year follow-up. At 5, 7, and 9 years, the survival rates were 99.8%, 94.5%, and 74.5%, respectively. It was dependent on either a decrease in IKDC or a progression of radiographic OA with Kellgren-Lawrence scores. Advanced age and the existence of bipolar kissing lesion were linked to notably inferior results. Furthermore, a greater quantity of MSCs was linked to significantly improved outcomes following MSC implantation. Consequently, the implantation of MSCs yielded promising results, demonstrating a satisfactory duration of symptom alleviation during the midterm follow-up period in patients diagnosed with early knee OA.[17]

Both Kim et al and Kim et al converges with the aim to evaluate the effectiveness of mesenchymal stem cell (MSC) implantation as a therapeutic approach for knee OA and related cartilage lesions. Both studies share the common objective of assessing the clinical results of therapies utilising MSCs through the standardised scoring systems. These scores include the international knee documentation committee (IKDC), Tegner activity scale, Lysholm Score, and KOOS. In both studies, radiographic examinations are performed to evaluate the course of the disease and the alignment of the knee joint. Although the two trials employ distinct methodology and interventions, they both reported that the potential of MSC therapy in enhancing patient outcomes in the management of knee OA was beneficial among patients of articular lesions.[16,17]

The study conducted a comparative analysis of clinical and second-look arthroscopic outcomes in cases of medial compartmental knee OA. It specifically focused on the augmentation of bone marrow aspirate concentrate (BMAC) and the implantation of human umbilical cord blood-derived mesenchymal stromal cells (hUCB-MSC) in high tibial osteotomy (HTO). Between June 2014 and September 2018, a total of 176 patients underwent a combination of HTO and either a BMAC or hUCB-MSC surgery. The surgery was scheduled for medial compartment OA (Kellgren-Lawrence grade 3). The minimum follow-up period for these patients was 2 years. Several incisions were made at the locations of cartilage defects in the medial femoral condyle (MFC). Subsequently, BMAC or hUCB-MSCs were produced and combined with scafolds for implantation into the MFC lesions. After an average follow-up period of 33 months, both groups showed significant improvements in clinical outcomes, including IKDC, KOOS, SF-36, and Tegner activity scores. The hUCB-MSC group exhibited superior healing of regenerated cartilage compared to the BMAC group, as observed in the second-look arthroscopy. Furthermore, there was a strong correlation between ICRS CRA grades at second-look arthroscopy and clinical results. The study concluded that both interventions yielded comparable and dependable results in relation to alleviation of pain, functional assessments, and overall quality of life. Nevertheless, the efficacy of hUCB-MSC implantation surpassed that of BMAC augmentation in the context of articular cartilage regeneration.[18]

There are various ethical issues identified such as utilization of tools. The tools like Lysholm score, KOOS, and Kanamiya grades used in the studies to evaluate clinical outcomes for regenerating cartilage therapy do not indicate overall health of patient. It is required to describe the patient's overall health and postoperative status are by these evaluation techniques. Any biases or errors in these evaluations might distort clinical judgement and affect patient care. Getting informed consent from patients requires making sure they are aware of the potential hazards and limitations of these treatments.[16]

There are ethical issues associated with use of allogenic umbilical cord blood-derived mesenchymal stromal cell (UCB-MSC) implantation for cartilage regeneration. Allogenic cells require ethical approval due to the possibility of immunological rejection or unfavourable recipient reactions. To reduce these hazards, appropriate tissue matching, donor screening, and immunosuppressive medication administration are crucial.

Maintaining ethical standards in regenerative medicine research and practice requires making sure patients are properly informed about the potential advantages and disadvantages of treatment choices. The decisions about their care are made with their best interests in mind.[18]

Table 2: Summary of findings.

References	N	Age (in years)	Groups	Lesions/ procedure	Cell type	Cell delivery method	Cell source	Dosage	Follow up	Outcome
Yang et al, 2021[18]	176	56.5	Human umbilical cord blood-derived mesenchymal stromal cell (hUCB-MSC)		hUCB-MSCs)	4% HA (CARTISTEM ®)	Allogenic	500 mL/cm^2	33 months	At a mean follow-up of 33 months, both treatments yielded comparable clinical results, with hUCB-MSC implantation demonstrating greater efficacy in restoring articular cartilage compared to BMAC augmentation.
			Bone marrow aspirate concentrate (BMAC) augmentation	Full-thickness cartilage lesion						
Song et al, 2020[19]	128	>60		Full-thickness cartilage lesion (grade I-III)	UCBMSCs	4% HA (CARTISTEM ®)	Allogenic	2:5×106 cells/cm^2	24 months	Allogeneic UCBMSCs made OA joints much less painful and improved their ability to work which was hindered due to articular lesion.
Song et al, 2020[20]	125	58.3		Full-thickness cartilage lesion (grade IV)	hUCB-MSCs	4% HA (CARTISTEM ®)	Allogenic	500 µL/cm^2	36 months	Implanting hUCB-MSCs along with HTO is a good way to treat people with medial compartment arthritis along with varus deformity. The clinical results for patients get better when cartilage regenerate.
Kim et al, 2019[16]	80	55.6	MSC group	Grade III-IV lesions	Mesenchymal stem cell	Greenplast kit glue	Adipose tissue from patients	4.7×106 stem cells	27 months	The utilisation of MSCs in conjunction with allogenic cartilage exhibits superiority over the implantation of MSCs in isolation for cartilage regeneration, resulting in enhanced clinical outcomes.
		56.1	MSC-AC group		Mesenchymal stem cell with allogenic cartilage	MegaCartilage	alogenic			
Kim et al, 2020[17]	467	61.1		Full-thickness cartilage lesion	MSCs	Greenplast kit glue	Adipose tissue from patients	8.45×108 cells	Nine years	MSC implantation yielded promising results with a satisfactory duration of symptom alleviation during the midterm follow-up in individuals diagnosed with early knee OA. The failure of MSC implantation was found to be associated with independent parameters such as patient age, existence of bipolar kissing lesion, and number of MSCs.

DISCUSSION

It has been demonstrated that that cartilage lesions introduced with the intervention of stem cells showed improvement. Jung et al research demonstrated that cartilage was regenerated in MFC and MTP after second-look arthroscopy following medial opening-wedge HTO. Without undergoing cartilage regeneration surgery, we think that decreased joint stress of the medial compartment following HTO creates an environment conducive to cartilage regeneration, even though the regenerated cartilage is primarily immature. In order to improve inadequate cartilage repair, MSCs have been injected or implanted together with HTO.[21]

Wong et al. looked into the injection of BM-derived MSCs with HA. In comparison to the control group, they reported better short-term results and MOCART (magnetic resonance observation of cartilage repair tissue) ratings.[22] In Koh et al study, a group receiving an injection of platelet-rich plasma (PRP) and concurrent HTO was contrasted with a group receiving a dosage of PRP, HTO, and an extra infusion of MSCs produced from adipose tissue. Their findings showed that, in comparison to the group receiving a PRP injection alone, the group receiving an MSC injection had better clinical outcomes and cartilage recovery.[23]

According to Kim et al injecting MSCs generated from adipose tissue into 50 MCOA patients resulted in better clinical outcomes than using HTO alone.

It was revealed that regenerated cartilage altered clinical outcomes in patients with full-thickness articular cartilage lesion of ICRS grade IV with more than 4 cm^2 in the medial compartment of the knee, as well as varus deformity of more than 5°.[24]

Limitations

There are some limitations that might compromise its validity and generalizability. Theoretical constraints encompass heterogeneity in included research. It also include biases in the study selection and interpretation, such as publication bias. Methodological flaws include irregular reporting and inadequate assessment of potential bias sources. Lack of standardised outcome measurements also acts as limitation. Improving validity and applicability of the review, it is required to address these constraints through strict study selection and critical evaluation.

CONCLUSION

The stem cell therapy in the treatment of articular cartilage lesions has great potential. It enhances the management and treatment outcomes for individuals afflicted with cartilage abnormalities. It is beneficial particularly those diagnosed with OA. Research has demonstrated encouraging outcomes, such as alleviation of pain and improvement in functionality. It acts as a therapy for regeneration of cartilage in individuals with cartilage abnormalities such as lesions. Additional investigation is required to enhance therapy regimens, encompassing cell dosage, delivery techniques, and supplementary medicines. The use of stem cell therapies necessitates the imperative collaboration among researchers, doctors, regulatory agencies, and industrial partners.

Recommendations

Long-term follow-up studies are advised for stem cell therapy for articular cartilage defects such as lesions. Research on the comparative effectiveness of various stem cell types, delivery systems, and supplementary therapies has to be done. Establishment of standardised outcome measures is necessary to enable cross-study comparability. In order to comprehend molecular mechanisms underlying stem cell therapy for cartilage regeneration, mechanistic investigations ought to be carried out. Approaches to personalised medicine should be investigated. It can help pave way to customise stem cell-based therapies to the unique needs of each patient. Thorough testing, clinical trials, regulatory approval, and evidence-based guidelines should all be used to help translate research into clinical practice. For patient safety and regulatory compliance, ethical and legal issues need to be taken into account. This multimodal strategy will enhance the accessibility, safety, and effectiveness of stem cell-based therapies for articular cartilage lesions.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Suárez KM, Zea CAP, Vera MDF, Rodríguez BSP, Garces AJZ, Jijón ESV, et al. Advances in stem cell therapy for articular cartilage lesions: clinical evidence and future directions: a systematic review. Int J Res Orthop 2024;10:647-54.