

SYSTEMATIC REVIEW

Intra Articular Injection of Mesenchymal Stem Cells in Osteoarthritis of the Knee Joint: A Systematic Study

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Abstract: Treatment of osteoarthritis in the knee joint is carried out by sharing efforts. In addition to pharmacological therapy, it is also carried out therapy with the method of intra-articular injection of mesenchymal stem cells directly into the knee joint. This systematic study aims to find out the extent to which this method has been studied as well as the benefits of intra-articular knee joint by means of mesenchymal stem cells. This study was conducted as a systematic study by searching journal literature through the Google Scholar application with the keyword *intra articular injection mesenchymal stem cells on knee osteoarthritis* in the last 5 years, using a prism diagram classification system in article selection. The results of the selection found 41 articles that were included in the inclusion criteria. The results of the study found that there have been many studies of intra-articular injection therapy of mesenchymal stem cells from various sources. Research was carried out both pre-clinical and clinical, and assessment methods were carried out with various methods to see the results of the therapy given, and 90% showed the results of structural, functional, and clinical improvement of the knee joint. From the results of these studies, it is concluded that there have been many studies conducted and most have shown that this method provides benefits.

Keywords: Intra-articular injection, osteoarthritis of the knee joint, mesenchymal stem cells

INTRODUCTION

Osteoarthritis (OA) of the knee joint is commonly found in the community and is characterized by pain and impaired function in the knee joint, which has a serious impact on the quality of life of the sufferer.¹ A study in China revealed that the incidence of OA in the world is estimated at 203 per 10,000 people per year, with an estimated prevalence of about 16%.¹ In Indonesia, the prevalence of knee joint OA

in men ranged from 15% and 12% in women in 2010. At that time, it was estimated that the population of Indonesia amounted to 225 million people.² Management of OA therapy of the knee joint consists of pharmacological therapy using drugs of the *disease-modifying osteoarthritis drugs* (DMOADs) group, in which there are analgesic groups, corticosteroids, and monoclonal antibodies against nerve growth factor class drugs that

are given systemically and topically.³ In addition, there are also non-pharmacological therapies such as physiotherapy and acupuncture therapy.^{4,5} However, the management of pharmacological and non-pharmacological therapies that exist only shows short-term benefits and is symptomatic. So, currently, regeneration therapies have begun to be developed with the use of stem cells that are expected to treat the OA of the knee joint and it has proven to be an effective etiology therapy. This systematic study aims to determine the extent to which this method has been studied as well as the benefits of intra-articular injection therapy of the knee joint using mesenchymal stem cells in cases of knee joint OA.

METHOD

The results of the research are published in international journals with a date range of 2017 to 2022. Literature was searched using the Google Scholar search app, using the keyword "*Injection Intra-articular Mesenchymal Stem Cells*". The studies included in the inclusion criteria are articles with a time span of 2017 to 2022; both article research and literature review; and meta-analysis that use human and animal subjects and apply the use of mesenchymal stem cells by intra-articular injection to the knee joint in subjects suffering from OA of the knee joint naturally and in experimental animals conditioned to suffer from knee joint OA.

RESULT

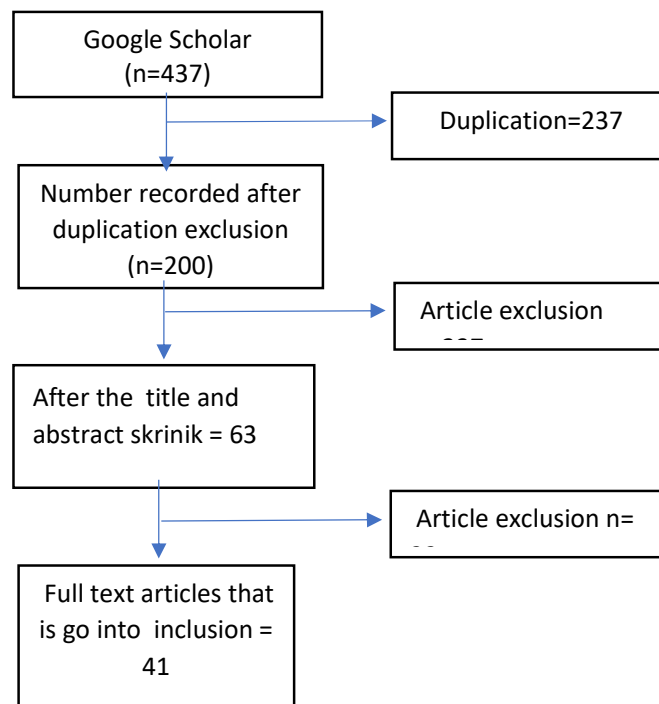


Figure 1. Prism Diagram

Table 1. Literature Search Results

No	Writer	Country As long as	Study	Mesenchymal Stem Cell Source	Independent Variables	Conclusion
1	Song Y <i>et al</i> ⁶	Chinese	Meta analysis	Bone marrow Placenta Adipose Peripheral blood	<ul style="list-style-type: none"> • VAS • WOMAC • <i>Adverse Events</i> • KOOS • SF 39 	Mesenchymal stem cell injection in the knee joint is effective in relieving pain and providing functional improvement in knee OA patients, more detailed research with a larger number of research samples is required.
2	Matteo BD <i>et al</i> ⁷	Italian	Review the article	Bone marrow	<ul style="list-style-type: none"> • NPS • Radiograph • bone marrow lesion volume • KSS • OKS, • WOMAC • Vas • ICOAP • Algometer, • Global patient satisfaction, • Participant-reported numeric pain rating scale, • LEFS • IKDC, SF-36 • Lys Holm 	The use of mesenchymal stem cells using <i>the bone marrow aspirate concentrate</i> (BMAC) and <i>stromal vascular fraction</i> (SVF) methods is considered safe and has several benefits in the short term.
3	Yubo M <i>et al</i> ⁸	Chinese	Meta analysis	Bone marrow Adipose Peripheral blood	<ul style="list-style-type: none"> • VAS • IKDC • WOMAC • Lequesne • Lys Holm • Tegner • Toxicity • Adverse reaction 	Overall, mesenchymal stem cell transplantation therapy has shown safety and is potentially good as an effective clinical therapy in patients with OA in the knee.
4	Doyle EC <i>et al</i> ⁹	English	Review the article	Bone marrow	<ul style="list-style-type: none"> • WOMAC • MRI • Vas • Lequesne • PCI 	Overall, the benefits of intra-articular injection of mesenchymal stem cells are considered to be more important than side effects, thus this therapy may be considered as a therapy in the future. Further research is still needed to realize this.

5	Wang AT <i>et al</i> ¹⁰	Chinese	Review the article	Bone marrow Adipose	<ul style="list-style-type: none"> • Vase • WOMAC • MRI • KOOS • X-ray • Walking distance • Lequesne • Knee motion 	Systematic reviews in clinical trials convinced us that mesenchymal stem cells are relatively safe at intra-vascular and intra-articular injection administration, but further research is still needed with a larger number of samples.
6	Freitag J <i>et al</i> ¹¹	Australia	Rct	Adipose	<ul style="list-style-type: none"> • MRI • NPRS • WOMAC • KOOS • MOAK 	<i>Autologous adipose-derived mesenchymal stem cells (ADMSC)</i> demonstrate safe and effective therapy for knee OA and have the potential to prevent disease progression.
7	Wang Y <i>et al</i> ¹²	Chinese	Experimental studies (pre-clinical)	Embryonic	<ul style="list-style-type: none"> • <i>Collagen type II synthesis,</i> • ADMTS5 	<i>Embryonic injection of mesenchymal stem cells (ESC-MSCs)</i> reduces the process of digestion and matrix degradation in the medial meniscus (DMM) destabilization model.
8	Iijima H <i>et al</i> ¹³	Japanese	Meta analysis	Bone marrow Adipose	<ul style="list-style-type: none"> • WOMAC • VAS • KSS • NPS • IKDC • Tegner activity scale • ICRS • KOOS • Pga • SF-36 • Lysholm 	Mesenchymal stem cell therapy by intra-articular injection and arthroscopic implantation provides a significant improvement in knee OA pain, physical function, and cartilage quality, and shows no severe side effects. However, a higher quality RCT is still required.
9	Kim YS <i>et al</i> ¹⁴	South Korea	Experimental pre-clinical	Human synovial	<ul style="list-style-type: none"> • MRI • Histopathology 	Intra-articular injections of <i>human synovium-derived MSCs (hSD-MSCs)</i> improve OA progressivity in experimental animals by restoring cartilage, accelerating matrix extracellular synthesis (ECM), and inhibiting inflammatory responses
10	Xing D <i>et al</i> ¹⁵	Chinese	Experimental pre-clinical	Bone marrow, synovial	<ul style="list-style-type: none"> • Gros morphology • Histology • Immunohistochemistry • X-ray • Behavior 	We do not yet have complete confidence in recommending mesenchymal stem cell injection for knee osteoarthritis.
11	Bastos R <i>et al</i> ¹⁶	Portugal	Clinical experiments	Spinal cord	<ul style="list-style-type: none"> • KOOS 	<i>Intra-articular injection of bone marrow derived culture expanded MSCs</i> with or

12	Hernigou <i>et al</i> ¹⁷	France	Rct	Bone marrow	<ul style="list-style-type: none"> • KSS • VAS • X-ray 	<p>without the addition of <i>platelet rich plasma</i> (PRP) is effective in improving function and reducing symptoms of knee OA in 12 month <i>follow up</i>. Implantation of mesenchymal stem cells in the sub-consular bone in the knee OA is more effective at delaying <i>Total Knee Arthroplasty</i> (TKA) compared to intra-articular dosing injection of the contra lateral knee at <i>the</i> same OA grade.</p>
13	Kim SH <i>et al</i> ¹⁸	South Korea	Meta analysis	Bone marrow Adipose	<ul style="list-style-type: none"> • VAS • WOMAC • Lysholm • MRI 	<p>This meta-analysis shows that intra-articular mesenchymal stem cells have limited evidence for pain relief and functional improvement in knee OA.</p>
14	Migliorini F <i>et al</i> ¹⁹	German	Systematic study	Bone marrow Adipose	<ul style="list-style-type: none"> • WOMAC • KOOS • <i>Walking distance</i> 	<p>From systematic studies, it is reported that mesenchymal stem cell infiltration for knee OA may represent a viable option that leads to clinical and functional improvement regardless of the source of mesenchymal stem cells. Patients who were treated as early as possible in the early phases of degeneration reportedly showed significant improvements. The pain and functional scales improved, thus leading to significant improvements in the study subjects.</p>
15	Wang J <i>et al</i> ²⁰	Chinese	Meta analysis	Bone marrow, Placenta	<ul style="list-style-type: none"> • VAS • WOMAC 	<p>Overall, mesenchymal stem cell-based therapy is a relatively safe therapy with the potential for OA therapy, with positive evidence of pain reduction and improvement of knee function. The use of low doses (25 million) and stem cells derived from adipose tends to give better results. But further research is still needed.</p>
16	Choi S <i>et al</i> ²¹	Korean	Experimental preclinical	Adipose	<ul style="list-style-type: none"> • Gross morphology, • Histology, • Immunohistochemistry 	<p>Intra-articular injection of mesenchymal stem cell adipose MSCs decreases the progressivity and extent of OA markedly.</p>

17	Bertoni L <i>et al</i> ²²	France	Experimental pre-clinical	Bone marrow Placenta	<ul style="list-style-type: none"> • Clinical • Ultrasound 	These studies have shown that injections in healthy joints in the same individual of allogeneic mesenchymal stem cells of the bone marrow induce synovial effusion significantly.
18	Han Y <i>et al</i> ²³	Chinese	Experimental pre-clinical	Adipose	<ul style="list-style-type: none"> • ICRS 	<i>Intra-patellar fat pad</i> (IPFP) MSCs feature an effective strategy to stimulate intra-articular cartilage regeneration.
19	McIntyre JA <i>et al</i> ²⁴	America	Systematic study	Bone marrow Adipose Synovial tissue Peripheral blood	<ul style="list-style-type: none"> • X Ray • MRI • Arthroscopy 	This study provides strong evidence that <i>intra-articular autologous MSC therapy</i> is a safe therapy and has many positive clinical effects.
20	Tan SHS <i>et al</i> ²⁵	Singapore	meta analysis	Bone marrow	<ul style="list-style-type: none"> • VAS • WOMAC 	Intra-articular injection of mesenchymal stem cells of the bone marrow without additional therapy is able to relieve pain and improve joint function in knee OA.
21	Zeng WN <i>et al</i> ²⁶	Chinese	Experimental pre-clinical	Bone marrow	<ul style="list-style-type: none"> • X-RAY • Behavioral • Histology 	<i>The KGN-enhanced BMSCs</i> showed a marked capacity for improvements in chondrogenesis and cartilage of the knee joint.
22	Zhang R <i>et al</i> ²⁷	Chinese	Experimental pre-clinical	Adipose	<ul style="list-style-type: none"> • Histology • Immunofluorescence • AORSI 	Intra-articular injection of adipose mesenchymal stem cells gradually alleviates the process of cartilage damage, reduces the <i>International Research Society (OARS)</i> Osteoarthritis Score and Mankin Score, and reduces the expression of Matrix Metalloproteinase 13 at different stages in the experimental rabbit OA model. Allogenic Adipose Mesenchymal Stem Cells do not cause side effects.
23	Xia T <i>et al</i> ²⁸	Chinese	Experimental pre-clinical	Bone marrow	<ul style="list-style-type: none"> • MRI • X-RAY 	There was no difference between the treatment of control and intra-articular injection of BMSCs in the knees of pigs.
24	Bastos R <i>et al</i> ²⁹	Brazil	Clinical experiments	Bone marrow	<ul style="list-style-type: none"> • KOOS 	Intra-articular injection of mesenchymal stem cells singularly or in combination with platelet rich plasma (PRP) is safe and has a good effect

25	Cheng JH <i>et al</i> ³⁰	Chinese	Experimental pre-clinical	Adipose	<ul style="list-style-type: none"> OARSI 	<p>on reducing signs and symptoms in knee OA patients. The use of <i>adipose-derived mesenchymal stem cells</i> (ADSC-CM) and <i>shockwave</i> (SW) improves the expression of cytokine inflammation and inflammation induced by <i>bone morphogenetic proteins</i> (BMPs) to maintain joint cartilage in joints with OA.</p>
26	Zhang Q <i>et al</i> ³¹	Chinese	Experimental pre-clinical	Placenta	<ul style="list-style-type: none"> Histopathology Mankin score Immunohistochemistry 	<p><i>Umbilical cord mesenchymal stem cells</i> (UC-MSCs) repair OA-inducing <i>monosodium iodoacetate</i> (MIA) by preventing cartilage damage, repairing chondrocyte proliferation and inhibiting inflammatory responses, which implies that human UC MSCs promise strategies for OA treatment.</p>
27	Hsu YK <i>et al</i> ³²	Japanese Taiwan	Experimental pre-clinical	Adipose	<ul style="list-style-type: none"> Gross inspection Histology 	<p><i>Intraarticular injection of platelet-rich fibrin releasates</i> (PRFr) plus <i>adipose-derived mesenchymal stem cells</i> (ADSCs) in the knee can reduce defects in cartilage by regenerating cartilage-like hyaline without any complications.</p>
28	Liu XW <i>et al</i> ³³	Chinese	Experimental pre-clinic	Adipose	<ul style="list-style-type: none"> Histology 	<p><i>Intraarticular injection of adipose-derived mesenchymal stem cells</i> (ADMSCs) plays a role in cartilage repair in knee OA through the <i>Notch1/Jagged 1 signaling pathway</i>.</p>
29	Ha CW <i>et al</i> ³⁴	Korean	Systematic study	Bone marrow Adipose Placenta	<ul style="list-style-type: none"> MRI Arthroscopy Vase WOMAC KSS Lysholm score KOOS SAS PGA Tegner IKDC SF-36 Lequesne HSS 	<p>Intra-articular injection of mesenchymal stem cells provides improvements in pain and function in knee OA in the short term (<28 months). In many cases, some efficacy of mesenchymal stem cells has been shown in the improvement of cartilage in knee OA, but evidence of clinical efficacy and improvement of cartilage in intra-articular injection of mesenchymal stem cells is still limited.</p>
30	Soltani SK <i>et al</i> ³⁵	Iran	Rct	Placenta	<ul style="list-style-type: none"> Vase KOOS 	<p>A single intra-articular injection of allogenic placental</p>

					<ul style="list-style-type: none"> • Rom • Mri 	mesenchymal stem cells (MSCs) on knee OA was found to be safe and resulted in clinical improvement within 24 weeks.
31	Shin YS <i>et al</i> ³⁶	Korean	Meta analysis	Bone marrow	<ul style="list-style-type: none"> • Vase • WOMAC • Lysholm score • HSS Score • Rom • WORMS • Pci 	<i>MSCs from bone marrow are viable as alternative therapies for knee OA, but a long-term, high-quality RCT is still needed to confirm their clinical benefits.</i>
32	Maheshwer B <i>et al</i> ³⁷	America	Meta Analysis	Bone marrow Adipose	<ul style="list-style-type: none"> • Vase • KOOS • WOMAC • Lysholm score 	The results of the standardized set of deficiency means (SMD) showed that there was a significant effect of MSC therapy on improving the physiological function of the joints but not on the pain reduction effect. The benefits of MSC therapy were seen in patients who also received surgical therapy simultaneously. MSC therapy has a significant impact on cartilage volume but not on cartilage quality.
33	Ma W <i>et al</i> ³⁸	Chinese	Meta analysis	Bone marrow Adipose	<ul style="list-style-type: none"> • Vase • WOMAC 	Intra-articular injection of MSCs is effective and safe for pain relief and improvement of motor function in patients with knee OA in the short term
34	Zia Z <i>et al</i> ³⁹	Chinese	Experimental preclinical	Rabbit synovial fluid	<ul style="list-style-type: none"> • Gros Morphology • Histology 	<i>Autologous undifferentiated rb SF-MSCs are beneficial for the regeneration of joint cartilage in cartilage defect therapy</i>
35	Espinosa JML <i>et al</i> ⁴⁰	Spanish	Rct	Bone marrow	<ul style="list-style-type: none"> • Vase • WOMAC 	Single intra-articular injection of <i>vitro autologous</i> BM-MSCs is a safe and possible procedure that results in clinical improvement and function in cases of OA of the knee joint.
36	Kim YS <i>et al</i> ⁴¹	South Korea	Rct	Adipose	<ul style="list-style-type: none"> • Vase • IKDC • Lysholm • X-ray 	The group of patients who received MSC therapy showed better results on <i>the Visual Analog Scale (VAS), International Knee Documentation Committee (IKDC) rating system, and Lysholm score at 1 year post-</i>

37	Wang Z <i>et al</i> ⁴²	Chinese	Experimental preclinical	Adipose	<ul style="list-style-type: none"> Flowcytometry Histology 	therapy MSCs compared to using hyaluronic acid. The study provides strong evidence that <i>human adipose tissue derived</i> MSCs (hAdMSCs) can be considered the leading therapeutic option for knee OA patients.
38	Matas J <i>et al</i> ⁴³	Chile	Rct	Placenta	<ul style="list-style-type: none"> WOMAC Vase 	<i>In a 1-year evaluation, intraarticular umbilical cord-derived</i> MSCs (UC-MSCs) injections were safe and better than hyaluronic acid therapy in knee OA.
39	Lee WS <i>et al</i> ⁴⁴	South Korea	Rct	Adipose	<ul style="list-style-type: none"> WOMAC 	<i>Intra-articular injection</i> of AD-MSCs provides satisfactory results for improved joint function and pain reduction in outpatient knee joint OA patients.
40	Feng C <i>et al</i> ⁴⁵	Chinese	Experimental pre-clinical	Adipose	<ul style="list-style-type: none"> Mri Histology CT Scan 	<i>Intra-articular injection of allogenic</i> ADMSCs combined with hyaluronic acid efficiently blocks the progressiveness of OA and triggers cartilage regeneration and is quite safe in monitoring for 14 days.
41	Wang XD <i>et al</i> ⁴⁶	Chinese	Experimental preclinical	Placenta	<ul style="list-style-type: none"> Expression levels 	<i>Intra-articular injection of allogenic</i> ADMSCs combined with hyaluronic acid efficiently blocks the progressiveness of OA and triggers cartilage regeneration and is quite safe in monitoring for 14 days.

DISCUSSION

Types of Studies

From the types of studies that have been carried out, in table 1, it can be seen

that there have been many pre-clinical and clinical studies, as well as found literature studies and meta-analyses, as can be seen in figure 2.

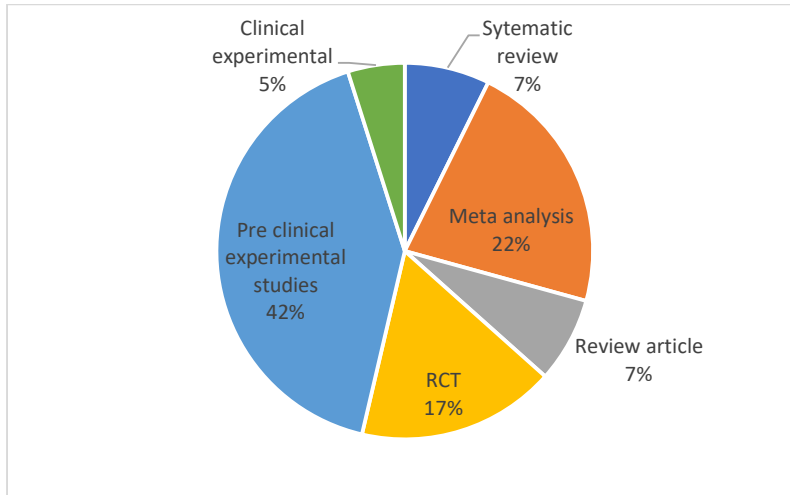


Figure 2. Types of studies that have been carried out

The country in which the research was carried out

The studies that have been carried out, if we look at figure 3, come from sharing countries where the most countries that have studied this method are China and Korea.

Mesenchymal Stem Cell Source

Figure 4 shows that the majority of mesenchymal stem cells used are derived from the spinal cord, adipose glands, placenta, and peripheral blood.

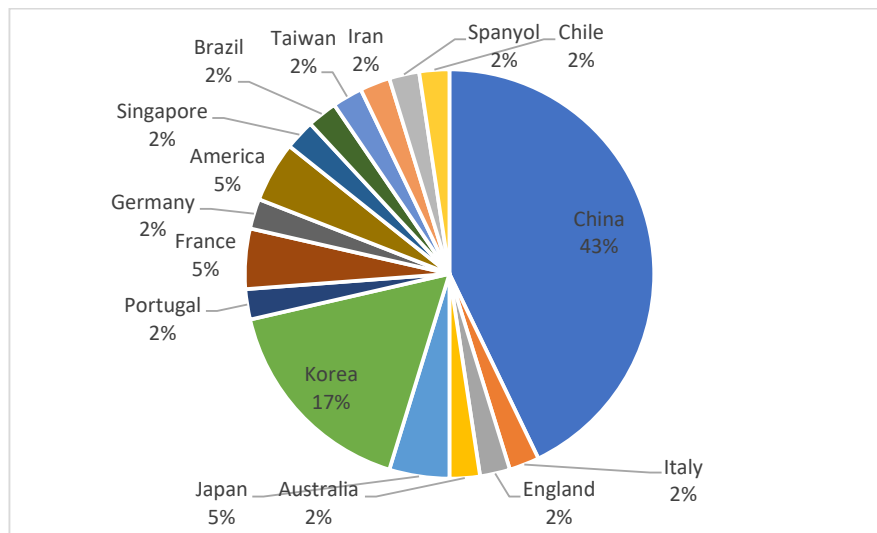


Figure 3. Country Where the Study Was Conducted

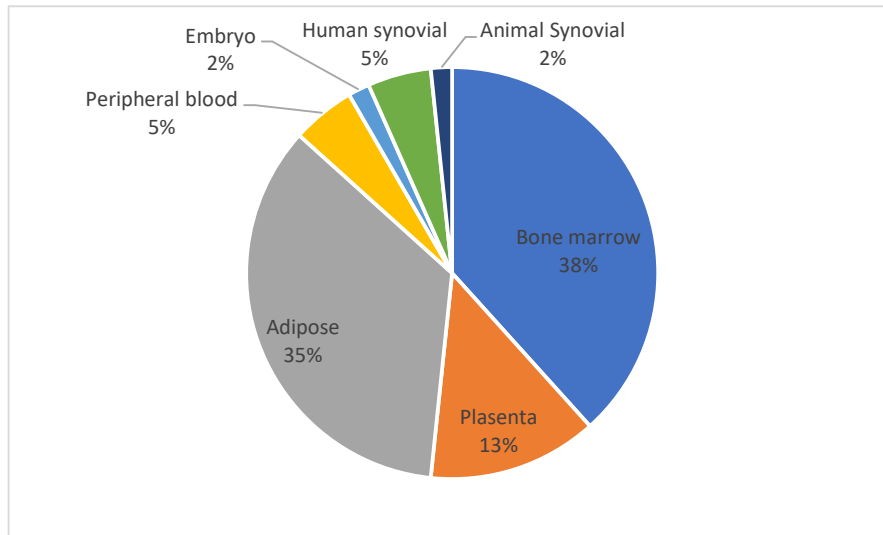


Figure 4. Mesenchymal Stem Cell Source

Evaluation Methods

Various methods are carried out to assess the results of the interventions

carried out. This can be seen in figure 5. The assessment method is selected based on the stage of research, namely pre-clinical research and clinical research.

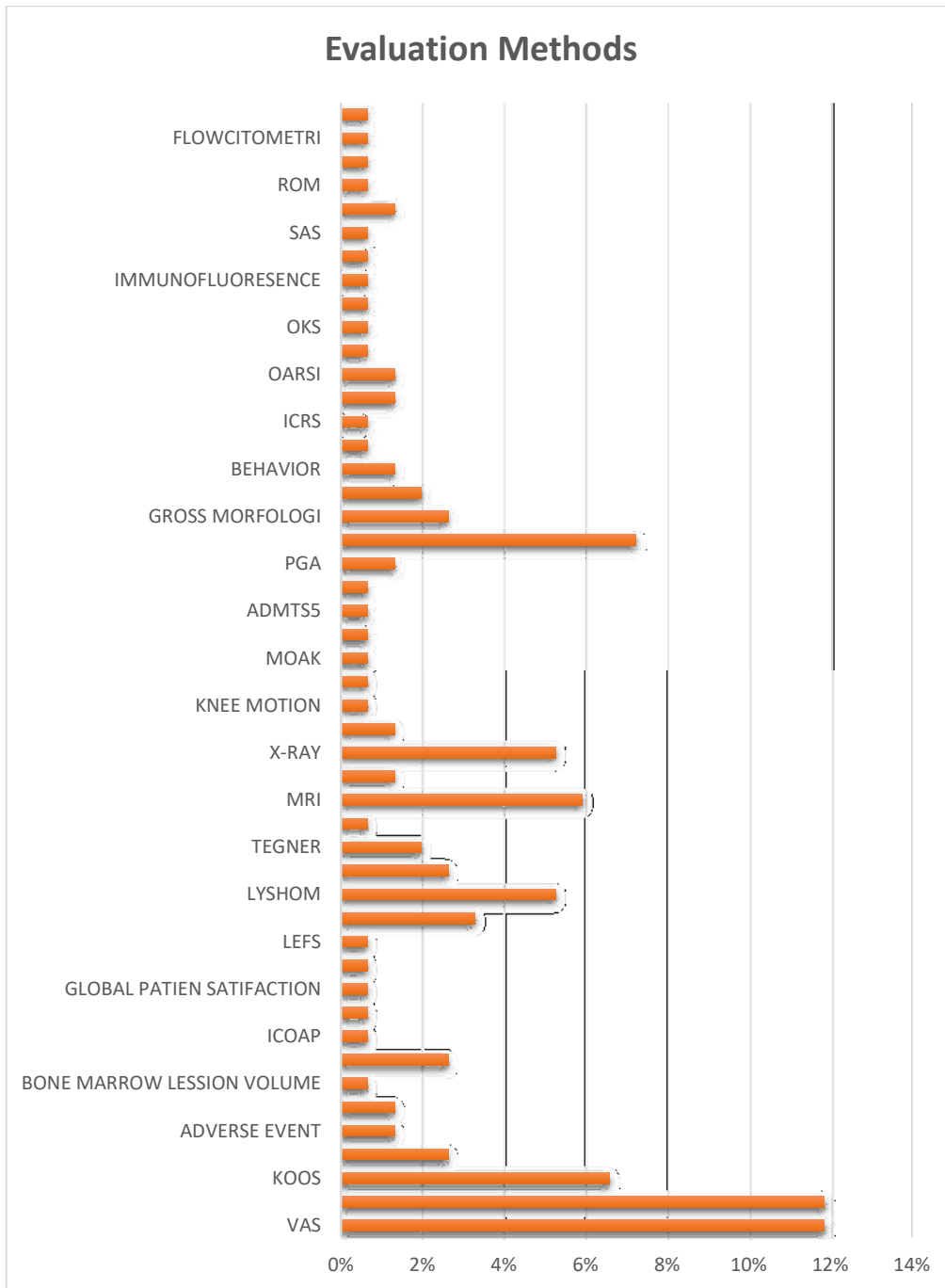


Figure 5. Assessment Methods

Evaluation of clinical research

Evaluation of clinical research using human subjects, using several methods.

Visual Analog Scale (VAS). This is certainly carried out in clinical studies involving humans as research subjects. The study was carried out by comparing VAS values before and after administration of intra-meaningful injection of mesenchymal stem cell snakes in the knee joints of patients who were evaluated for 3-6 months.

The Western Ontario and McMaster University Osteoarthritis Index (WOMAC). In WOMAC, the pain degree measurement index is associated with the activity performed by the patient. The higher the value, the more severe the disease suffered.

The Knee Injury and Osteoarthritis Outcome Score (KOOS) is a self-examination method to assess knee function that assesses five criteria, namely: pain, symptoms, activities of daily living, sport and recreation function, and knee-related quality of life. This score uses the numbers 0-100. A score of 0 is interpreted as a very serious problem in the knee, while the number 100 indicates a normal condition. It also assesses the degree of pain as well as the limitation of activity that occurs in patients with knee joint arthritis.⁴⁷

The Lysholm score or lysholm knee scoring is a measuring tool method used to assess the condition of the knee by assessing 8 aspects, namely instability (25 points), pain (25 points), stiffness (15 points), climbing stairs (10 points), swelling (10 points), need for help (5 points), squatting (5 points), weakness (5 points). This scale uses a range of values from 0 (which describes a bad condition) to a value of 100 (normal condition).⁴⁸

Hospital for Special Surgery Knee Rating Scale (HSS), This scale evaluates pain (30 points), function (22 points), movement (18 points), muscle strength (10 points), bending disturbances (10 points), instability (10 points), and limitations, with > 85 being perfect, 70-84 good grades, 60-69 fair grades, and 60 bad grades.⁴⁹

The International Knee Documentation Committee (IKDC) is a score used to perform assessments on knee joint health. The criteria that become the assessment are symptoms in the knee (7 symptoms) assessment of the knee joint (2 items), exercise activity (2 items), and the range of scores from 0 (lowest function level or highest symptom level) to 100 points (highest function level and lowest symptom level).⁵⁰

The Hospital for Special Surgery Knee-Rating Scale (HSS) in it assesses pain (30 points), function (22 points), range of movement (range of motion) (18 points), muscle strength (10 points), joint stiffness/*flexion deformity* (10 points), instability (10 points), >85 perfect scores, 70-84 good, 60-69 averages, <60 bad.⁵¹

The Knee Range of Motion (ROM) is an assessment of the extent to which the knee joint can bend and straighten. The ability of the knee is assessed both actively and passively. The active assessment includes the ability of the knee joint to perform maximum flexion (135°), extensions (0°), internal rotation (10°), and external rotation (30-400). On passive assessment, passive knee alignment was assessed with normal values > 1500 and passive knee joint extension (10°).

The Pain Coping Inventory (PCI) at this time was assessed at six points, namely pain

transformation, distraction, reduction demands, retreating, worrying, and resting.⁵²

The Whole Organ Magnetic Resonance Imaging Score (WORMS), the assessed aspects of the knee joint include the integrity of cartilage, articular, subchondral, bone marrow abnormalities, crucial ligaments, and meniscus integrity.⁵³

The Tegner Activity Scale (TAS) is a new level of scale that assesses activity based on work and exercise ability.⁵⁴

The Knee Society Score (KSS) is a score used to assess the function of the knee joint by assessing the presence or absence of pain, the flexibility ability of the knee joint, as well as functional abilities such as assessing the ability to walk normally and with workloads such as climbing stairs.⁵⁵

The Lysholm Knee Scoring Scale, has eight assessment criteria, namely: pain (25 points), instability (25 points), locking (15 points), swelling (10 points), limp (5 points), climbing (10 points), squatting (5 points), and need for support (5 points).⁵⁶

The Sports Activities Scale (SAS) is an 11-item scale that asks patients about how their symptoms affect their ability to perform sports and recreational activities (7 items).⁵⁷

Patient Global Assessment (PGA) is a self-assessment method to assess the body's ability of patients suffering from certain diseases to engage in physical activity.⁵⁸

The Tegner Activity Score is a method to assess the level of activity ability based on the ability to work and exercise.⁵⁹

The International Knee Documentation Committee (IKDC), an independent assessment with a questionnaire to assess the knee joint which includes three categories, namely the presence or absence of symptoms that appear, the ability to physical activity, and the function of the knee joint itself.⁶⁰

Short Form Health Survey (SF-36) is a type of independent questionnaire filled out by patients that included 36 questions about general health conditions, the presence or absence of activity limitations, physical health problems, emotional health problems, social activities, pain, energy, and emotions.⁶¹

The Lequesne index for knee osteoarthritis includes an independent questionnaire that assesses knee function, covering 3 things, namely the presence or absence of pain or discomfort, the ability to walk a distance, and the difficulty in carrying out daily activities.⁶²

Pre-Clinical Research Evaluation

In pre-clinical studies that use animals as research subjects, they evaluate the results of therapy using several methods.

Histology

In observations with a histological approach, researchers saw defects in cartilage that appeared due to degenerative processes in osteoarthritis.³⁹ After the intervention using MSC, researchers noticed the extent to which MSC was able to fill and regenerate cartilage defects that occurred.³⁹ Histological observations were made 8–12 weeks after the injection of mesenchymal stem cells into the knee joint.³⁹ Staining methods in histological

analysis were carried out using hematoxylin-eosin or safranin-O/fast green, toluidine blue, and immunohistochemistry. Then, quantitative evaluation was carried out to assess the thickness of cartilage and the ICRS score was used.^{45,28}

Behaviour

Assessing with a behavioral approach, the experimental animal was given ballast pads on the legs of the experimental animals and measurements of static inability were carried out using the Columbus instrument, in which the mice were placed in a room with both hind legs given ballast pads, then measurements were taken for 3 seconds in 3 separate measurements expressed in percentage of the ability of the hind legs to move.²⁶ In addition to ballast bearings, hot plate tests were also carried out by the hot *plate analgesia meter* method, in which mice were placed on hot plates, to be later observed for responses such as shaking, licking, or jumping.²⁶ The Columbus instruments themselves are trademarks of a set of instruments to monitor the behavior and physiology of the bodies of experimental animals.⁶³

X-Ray

The use of X-ray is carried out to assess the degree of OA and to evaluate the effectiveness of the use of mesenchymal stem cells in the knee joint.²⁸ Radiological evaluation uses the *Kellgren-Lawrence (K-L) grading system* assessment method.¹⁴ The radiology technique applied is with an *anteroposterior weight bearing view (AP)* where the position of the joint is at a 30 degree angle position.⁴¹

Ultrasound

The use of ultrasound (ultrasound) was carried out to assess the condition of the joints starting before the intervention of mesenchymal stem cells and after the serial administration of mesenchymal stem cells in one study result. The examination was carried out transversely and longitudinally using a linear transducer of magnitude 7.5MHz.²²

Expression of Collagen Type II and ADAMTS5

The injection of mesenchymal stem cells into the knee joint, with observation using immunohistochemistry methods, is seen to be able to increase collagen type II, which is the main component in the knee joint, as well as reduce the expression of ADAMTS5 (aggrecan-degrading enzyme 5), which is a sign of the process of tissue destruction in the body.¹²

Flowcytometer

A flowcytometer was used to see cell expression resulting from tissue culture and after interventions in the injection of mesenchymal stem cells into the knee joint.⁴²

Gros Observation

Observations were made on the joints of the study subjects after the injection of mesenchymal stem cells into the knee joint. The evaluation was carried out at 8 weeks to 12 weeks by performing surgery on the knees of the study subjects themselves. The researchers saw that there was a firm boundary between the healthy part covered by the MSC membrane and the deformed part.³⁹

MRI

The MRI method is used to evaluate after the injection of mesenchymal stem cells and evaluate the assessment of MRI

results using *the magnetic resonance observation of cartilage repair tissue (MOCART) scoring system*. In this method, photo observations are carried out by taking them sagittally.⁴⁵

Immunohistochemistry

Immunohistochemistry is used to see the expression of antigen proteins in cells so that they can identify what proteins appear after the intervention of certain substances. In the study on the effect of MSC infection on the knee joint, with the use of immunohistochemistry staining techniques, there was a decrease in the regulation of matrix metalloprotein-13 (MMP-13) and a disintegrin and metalloproteinase with thrombospondin motif 5 (ADAMTS-5) where both were signs of tissue degradation. In addition to

this technique, there was an increase in the expression of collagen type II and KI-67, a nonton core protein, which is a sign of proliferation cell.³¹

Clinical

Clinical evaluation of the study subjects was carried out by conducting an examination of their heart rate, respiratory frequency, body temperature, and appetite, which were monitored twice a day to see if there were signs of discomfort in the study subjects.²²

Study Results

Figure 6 depicts the majority of studies that show positive (beneficial) results on the improvement of the knee joint structurally, functionally, and clinically as evidenced by various assessments.

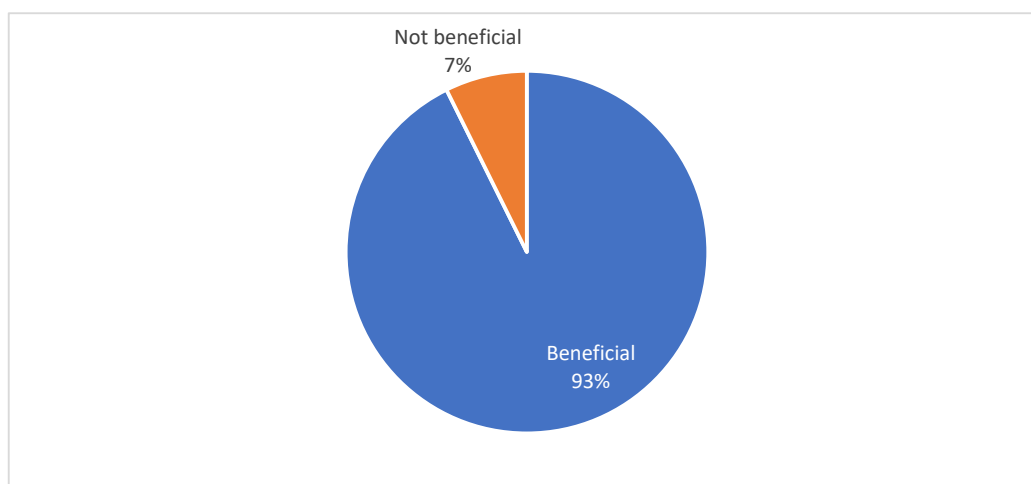


Figure 6. Study Results

CONCLUSION

It can be concluded that the method of intra-articular injection of mesenchymal stem cells has been widely studied in various countries, with the results of research showing that this method provides benefits for the improvement of the knee joint

structurally, functionally, and clinically in cases of osteoarthritis of the knee joint.

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