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Intra-articular administration of autologous and allogeneic mesenchymal stromal cells for knee osteoarthritis: a systematic review and meta-analysis of clinical studies

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Objective. To evaluate the efficacy and safety of intra-articular administration of autologous and allogeneic mesenchymal stromal cells in the treatment of knee osteoarthritis based on a systematic review and meta-analysis of clinical studies. **Methods.** A systematic review and meta-analysis were conducted in accordance with the PRISMA 2020 principles. The literature search was performed in PubMed, Scopus, Web of Science, and Cochrane Library databases for the period from 2010 to 2025. The qualitative analysis included 11 clinical studies evaluating the efficacy and/or safety of intra-articular mesenchymal stromal cell administration in patients with knee osteoarthritis. **Results.** The VAS meta-analysis included 4 controlled studies with a total of 87 participants, while the WOMAC meta-analysis included 3 controlled studies with a total of 67 participants. Intra-articular administration of mesenchymal stromal cells was associated with a statistically significant reduction in pain intensity according to the VAS score: $SMD = -1.09$; 95 % CI: -1.81 to -0.36 ; $p = 0.003$; $I^2 = 56$ %. A statistically significant improvement in functional status according to the WOMAC score was also observed: $SMD = -0.62$; 95 % CI: -1.19 to -0.05 ; $p = 0.03$; $I^2 = 22$ %. In most included studies, mesenchymal stromal cell therapy was well tolerated. The most commonly reported adverse events were transient local pain, swelling, or mild synovitis after injection. **Conclusions.** Intra-articular administration of mesenchymal stromal cells may represent a promising biological approach for the treatment of knee osteoarthritis, as it is associated with pain reduction and functional improvement.

Мета. Оцінити ефективність і безпеку внутрішньосуглобового застосування аутологічних та алогенних мезенхімальних стромальних клітин (МСК) у лікуванні пацієнтів з остеоартрозом колінного суглоба на основі систематичного огляду та метааналізу клінічних досліджень. **Методи.** Проведено систематичний огляд і метааналіз відповідно до принципів PRISMA 2020. Пошук літератури виконували в базах PubMed, Scopus, Web of Science та Cochrane Library за період 2010–2025 р. До якісного аналізу включено 11 клінічних досліджень, у яких оцінювали ефективність або безпеку внутрішньосуглобового застосування МСК за остеоартрозу колінного суглоба. **Результати.** До метааналізу за шкалою VAS було включено 4 контрольовані дослідження зі загальною кількістю 87 учасників, а за шкалою WOMAC — 3 (67 осіб). Внутрішньосуглобове застосування МСК асоціювалося зі статистично значущим зменшенням больового синдрому за шкалою VAS: $SMD = -1,09$; 95 % ДІ: $-1,81$ до $-0,36$; $p = 0,003$; $I^2 = 56$ %. Також встановлено статистично значуще покращення функціонального стану за шкалою WOMAC: $SMD = -0,62$; 95 % ДІ: $-1,19$ до $-0,05$; $p = 0,03$; $I^2 = 22$ %. У більшості включених робіт терапія характеризувалася доброю переносимістю. Найчастіше реєстрували короточасний локальний біль, набряк або транзиторний синовіт після ін'єкції. **Висновки.** Внутрішньосуглобове застосування мезенхімальних стромальних клітин може бути перспективним біологічним підходом до лікування остеоартрозу колінного суглоба, оскільки асоціюється зі зменшенням болю та покращенням функціонального стану. **Ключові слова.** Остеоартроз колінного суглоба, мезенхімальні стромальні клітини, аутологічні МСК, алогенні МСК, внутрішньосуглобове введення, VAS, WOMAC, метааналіз.

Keywords. Knee osteoarthritis, mesenchymal stromal cells, autologous MSCs, allogeneic MSCs, intra-articular injection, VAS, WOMAC, meta-analysis

Introduction

Osteoarthritis (OA) is a chronic degenerative joint disease characterized by progressive cartilage destruction, subchondral bone remodeling, and the development of chronic pain and functional limitations. According to the WHO, osteoarthritis is one of the leading causes of disability among people over 50 years of age. Intra-articular osteochondral lesions represent a significant clinical challenge because of their limited capacity for spontaneous regeneration and the risk of progressive osteoarthritis [1]. Traditional treatment includes pharmacotherapy (non-steroidal anti-inflammatory drugs, intra-articular hyaluronic acid injections, and corticosteroids), physiotherapy, and surgical interventions. However, none of these approaches directly addresses the underlying pathogenesis or promotes cartilage regeneration.

Mesenchymal stem cells (MSCs) have been actively investigated over the past two decades as a promising therapeutic approach because of their ability to differentiate into chondrogenic, osteogenic, and adipogenic cells, as well as their immunomodulatory and anti-inflammatory effects [2, 3]. MSCs are considered a promising biological therapy owing to their:

- regenerative potential, including stimulation of chondrogenesis;
- anti-inflammatory and immunomodulatory effects;
- ability to modify the microenvironment of the affected joint.

Currently, two main types of MSCs are used: autologous MSCs, obtained from the patient themselves, primarily from bone marrow or adipose tissue, and allogeneic MSCs, obtained from donors, including umbilical cord tissue, placenta, or bone marrow of healthy donors. Despite shared mechanisms of action, these sources differ substantially:

- autologous MSCs eliminate the risk of an immune response, but their quality depends on the patient's age and comorbidities [4, 5];
- allogeneic MSCs have greater proliferative potential and availability but raise concerns regarding immunogenicity and long-term safety [6].

Conducting a meta-analysis evaluating the efficacy and safety of autologous and allogeneic MSCs in the treatment of early-stage osteoarthritis may provide an objective assessment of the advantages of each approach and help identify areas for further research.

Aim: To evaluate the efficacy and safety of intra-articular administration of autologous and allo-

geneic mesenchymal stromal cells for the treatment of knee osteoarthritis through a systematic review and meta-analysis of clinical studies.

Materials and Methods

A systematic review and meta-analysis of clinical studies investigating the intra-articular administration of MSCs in patients with knee osteoarthritis were conducted. The study was performed in accordance with the principles of PRISMA 2020.

A literature search was conducted in PubMed, Scopus, Web of Science, and the Cochrane Library for studies published between 2010 and 2025. The following keywords and combinations thereof were used: “knee osteoarthritis”, “mesenchymal stem cells”, “mesenchymal stromal cells”, “autologous”, “allogeneic”, “bone marrow-derived”, “adipose-derived”, “umbilical cord-derived”, and “intra-articular injection”.

Clinical studies evaluating the efficacy or safety of autologous or allogeneic MSCs in patients with knee osteoarthritis were included in the qualitative analysis. The quantitative meta-analysis included only controlled studies with sufficient numerical data to calculate effect estimates for the VAS or WOMAC scales.

Inclusion criteria were as follows: clinical studies involving patients with knee osteoarthritis; administration of autologous or allogeneic MSCs with a clearly described cell source; intra-articular administration of MSCs; availability of clinical treatment outcomes; assessment of efficacy using the WOMAC, VAS, KOOS, or other validated clinical scales; and availability of a full-text publication in English.

Exclusion criteria were as follows: review articles without primary data; experimental and preclinical studies; studies without clinical outcome measures; duplicate publications; and articles with insufficient data for analysis.

Study Selection

The initial search identified 122 records: PubMed — 48, Scopus — 36, Web of Science — 27, and the Cochrane Library — 11. After removal of duplicates, 76 unique articles remained and were included in the screening process, during which titles and abstracts were assessed. At this stage, 54 publications were excluded. The main reasons for exclusion were a review article format without primary clinical data; experimental or preclinical study design; studies focused on cartilage repair in the absence of knee osteoarthritis or unrelated to MSC therapy; as well as conference materials and abstracts.

Twenty-two full-text publications were selected for detailed assessment. Following full-text evaluation, 11 studies were excluded because of the absence of relevant clinical outcome measures, insufficiently described cell sources, insufficient numerical data for further analysis, duplicated data, or study designs that did not meet the inclusion criteria.

Eleven clinical studies evaluating the efficacy or safety of intra-articular administration of autologous or allogeneic MSCs in patients with knee osteoarthritis were included in the qualitative systematic review.

For the quantitative meta-analysis, only controlled studies with sufficient numerical data reported as mean $\pm$ SD or data that could be converted to this format were included. Consequently, 4 controlled studies with a total of 87 participants were included in the VAS analysis, while 3 studies with a total of 67 participants were included in the WOMAC analysis. Studies without a control group or with incomplete numerical data were included in the qualitative analysis but were not used to construct the primary forest plots. The study selection process is presented in the PRISMA flow diagram (Fig. 1).

Risk of Bias Assessment

The risk of bias in randomized studies was assessed using the Cochrane Risk of Bias 2.0 (RoB 2) tool, whereas non-randomized studies were assessed using the Newcastle–Ottawa Scale (NOS). Most controlled studies were characterized by a low or moderate risk of bias. The main potential sources of bias were small sample sizes, differences in the type of control intervention, heterogeneity of the cellular products, and incomplete reporting of numerical outcome data.

Data Extraction

The following data were extracted from each study: author, year of publication, study design, MSC

type, cell source, number of patients, presence and type of control group, osteoarthritis severity according to the Kellgren–Lawrence classification, administration method, follow-up duration, clinical assessment scales, and adverse events.

For the quantitative analysis, final VAS and WOMAC scores in the MSC and control groups were used. When data were reported as the median and interquartile range (IQR), they were converted to mean $\pm$ SD using validated statistical methods in accordance with the recommendations of Wan et al. [7].

The primary endpoints for efficacy assessment were pain intensity measured using the VAS and functional status assessed using the WOMAC. Secondary outcomes included MRI findings, the frequency of adverse events, and the safety profile of the therapy.

Statistical Analysis

Statistical analyses were performed using Review Manager 5.4. For continuous variables, the standardized mean difference (SMD) with a 95 % confidence interval (CI) was used. Meta-analysis was performed using a random-effects model (DerSimonian–Laird), taking into account the expected clinical and methodological heterogeneity among the included studies.

Statistical analyses were performed using Review Manager 5.4. For continuous variables, the standardized mean difference (SMD) with a 95 % confidence interval (CI) was used. Meta-analysis was performed using a random-effects model (DerSimonian–Laird), taking into account the expected clinical and methodological heterogeneity among the included studies.

Heterogeneity was assessed using the I^2 statistic: $< 25\%$ — low, $25\text{--}50\%$ — moderate, and $> 50\%$ — high. Differences were considered statistically significant at $p < 0.05$.

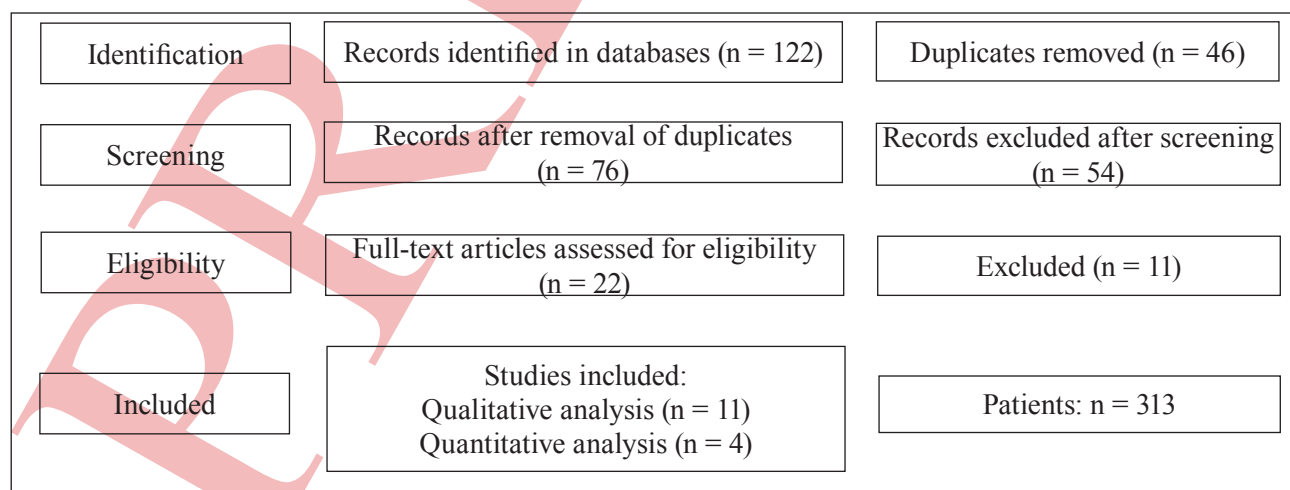


Fig. 1. PRISMA flow diagram

Data reported as the median and interquartile range (IQR) were converted to mean $\pm$ standard deviation according to the recommendations of Wan et al. [7].

Results

Characteristics of the Included Studies

Clinical studies evaluating the efficacy and safety of intra-articular administration of autologous or allogeneic MSCs in patients with knee osteoarthritis were included in the qualitative systematic review.

The included studies differed in study design, cell source, MSC type, presence of a control group, follow-up duration, and clinical assessment scales used. The most frequently reported outcome measures were VAS and WOMAC; some studies additionally as-

sessed KOOS, the Lequesne index, ICOAP, WOMS, and MRI parameters reflecting the structural status of the joint.

For the quantitative meta-analysis, only controlled studies with sufficient numerical data reported as mean $\pm$ SD or with data that could be calculated or converted to this format were selected. Studies without a control group or with incomplete numerical data were included in the qualitative analysis but were not used to construct the primary forest plots.

Because of methodological heterogeneity among the included studies and differences in the format of outcome reporting, the quantitative meta-analysis was performed only for controlled studies with sufficient numerical data for VAS and WOMAC outcomes. Other studies (Table 1) were included in

Table 1

Main characteristics of the clinical studies included in the qualitative systematic review

Author, year	Study design	MSC type	MSC source	n	Control group	OA grade (KL)	Follow-up period, months	Primary outcome indicator
C. H. Jo et al., 2014 [2]	Phase I/II proof-of-concept study	Autologous	AD-MSC	18	Absent	III–IV	6	WOMAC, VAS
L. Orozco et al., 2013 [8]	Pilot clinical study	Autologous	BM-MSC	12	Absent	II–IV	12	WOMAC, VAS, Lequesne
J. M. Lamo-Espinosa et al., 2016 [3]	Multicenter randomized phase I/II trial	Autologous	BM-MSC	30	Hyaluronic acid	II–III	12	WOMAC, VAS
W. S. Lee et al., 2019 [9]	Double-blind randomized placebo-controlled trial	Autologous	AD-MSC	24	Placebo	II–IV	6	WOMAC, VAS
J. Freitag et al., 2019 [10]	Randomized controlled trial	Autologous	AD-MSC	30	Conservative treatment	II–III	12	WOMAC, VAS
D. Kuah et al., 2018 [11]	Randomized controlled trial	Allogeneic	AD-MSC	20	Placebo	I–III	12	WOMAC, VAS
A. Vega et al., 2015 [6]	Randomized controlled trial	Allogeneic	BM-MSC	30	Hyaluronic acid	II–IV	12	WOMAC, VAS, MRI
P. K. Gupta et al., 2016 [4]	Randomized double-blind placebo-controlled multicenter trial	Allogeneic	BM-MSC	60	Placebo	II–III	12	WOMAC, VAS, ICOAP
J. Matas et al., 2018 [12]	Randomized phase I/II trial	Allogeneic	UC-MSC	26	Hyaluronic acid	I–III	12	WOMAC, VAS, WOMS
Freitag et al., 2024 [13]	Randomized controlled trial	Allogeneic	AD-MSC	40	Placebo	II–III	12	WOMAC, VAS, KOOS
M. Al Najar et al., 2017 [14]	Prospective clinical study	Autologous	BM-MSC	13	Absent	II–III	12	KOOS, VAS

the qualitative synthesis and used for a descriptive analysis of clinical efficacy, safety, and structural changes assessed by MRI.

Quantitative Meta-Analysis of VAS Scores

Four controlled studies with a total of 87 participants were included in the VAS meta-analysis. The analysis was performed using a random-effects model.

A statistically significant reduction in pain was observed in favor of MSC therapy compared with the control intervention: SMD = -1.09 ; 95% CI, -1.81 to -0.36 ; $p = 0.003$.

Between-study heterogeneity was moderate to high: $I^2 = 56\%$.

These findings indicate that intra-articular MSC administration is associated with a significant reduction in pain measured by the VAS compared with control treatment.

Quantitative Meta-Analysis of WOMAC Scores

Three controlled studies with a total of 67 participants were included in the WOMAC meta-analysis. The analysis was also performed using a random-effects model.

The meta-analysis demonstrated a statistically significant improvement in functional status in favor of MSC therapy compared with the control intervention: SMD = -0.62 ; 95 % CI, -1.19 to -0.05 ; $p = 0.03$.

Heterogeneity was low: $I^2 = 22\%$.

Thus, according to the WOMAC score, MSC therapy also demonstrated a statistically significant benefit compared with the control intervention.

Data Used for the Quantitative Analysis

Final VAS and WOMAC scores in the MSC and control groups were used for the quantitative analysis. When the standard deviation was not reported directly, it was calculated from the available statistical parameters or converted from median (IQR) according to the method described by Wan et al. [7] (Table 2).

This approach made it possible to include in the analysis only those studies for which a valid statistical comparison between MSC therapy and the control intervention was possible.

Studies Not Included in the Quantitative Meta-Analysis

Some articles were included only in the qualitative analysis. The main reasons for exclusion from the quantitative meta-analysis were the absence of a control group, incomplete numerical data, results reported only in graphical format, a different direction of scale interpretation, or the absence of a full text containing the required data.

In particular, the uncontrolled studies by C. H. Jo and L. Orozco et al. [2, 8] were not included in

Table 2

Data used for the quantitative meta-analysis in RevMan

Indicator	Study	MSC group, n	MSC mean $\pm$ SD	Control, n	Control mean $\pm$ SD	Follow-up period	Note
VAS	A. Vega et al., 2015 [6]	15	33.0 ± 23.24	15	51.0 ± 30.98	12 months	SD calculated from SE
VAS	J. Matas et al., 2018 [12]	9	2.4 ± 2.10	8	22.1 ± 9.80	12 months	MSC-2 vs HA
VAS	J. M. Lamo-Espinosa et al., 2016 [3]	10	2.0 ± 2.96	10	4.0 ± 1.48	12 months	mean $\pm$ SD converted from median (IQR)
VAS	P. K. Gupta et al., 2016 [4]	10	20.6 ± 19.7	10	39.7 ± 23.80	12 months	25M-group; SD used as proxy with baseline
WOMAC	A. Vega et al., 2015 [6]	15	28.0 ± 19.36	15	41.0 ± 23.24	12 months	SD calculated from SE
WOMAC	J. Matas et al., 2018 [12]	9	4.2 ± 3.90	8	15.2 ± 11.00	12 months	MSC-2 vs HA
WOMAC	J. M. Lamo-Espinosa et al., 2016 [3]	10	15.83 ± 5.19	10	18.17 ± 18.52	12 months	mean $\pm$ SD converted from median (IQR)

Notes: MSC — mesenchymal stromal cells; SD — standard deviation; SE — standard error; CI — confidence interval; HA — hyaluronic acid.

the primary forest plots but were considered in the qualitative assessment of the clinical efficacy of MSC therapy. The studies by W. S. Lee, D. Kuah, Y. Ao, Y. Freitag et al. [5, 9–11] were not included in the primary quantitative analysis because of insufficient or heterogeneous numerical data for standardized comparison.

Figure 2 demonstrates a statistically significant reduction in pain measured by the VAS in controlled studies in favor of MSC therapy. Negative SMD values indicate a benefit of MSC therapy compared with the control intervention. The pooled effect was $SMD = -1.09$; 95% CI, -1.81 to -0.36 ; $p = 0.003$; $I^2 = 56\%$.

Figure 3 illustrates the effect of MSC therapy on functional status measured by the WOMAC in controlled studies. Negative SMD values indicate an improvement in functional status in favor of MSC therapy. The pooled effect was $SMD = -0.62$; 95 % CI, -1.19 to -0.05 ; $p = 0.03$; $I^2 = 22\%$.

Safety

In most included studies, intra-articular administration of MSCs was well tolerated. The most frequently reported adverse events were transient local pain, swelling, or transient synovitis following injection. These events were generally mild or moderate and did not require treatment discontinuation (Tables 3 and 4).

Serious adverse events, such as septic arthritis, severe systemic infections, anaphylactic reactions,

or clinically significant immune-related complications, were generally not reported. However, because of the small sample sizes and limited follow-up duration, definitive assessment of long-term safety, particularly for allogeneic MSCs, requires further follow-up and longer-term studies.

MRI Results and Structural Changes

In some studies, MRI parameters assessing the condition of the articular cartilage and subchondral bone were also evaluated. Several studies reported stabilization or moderate improvement in the structural characteristics of articular cartilage following MSC therapy. At the same time, the MRI data were heterogeneous in terms of assessment methods, scales, and follow-up time points.

Due to the lack of standardized MRI protocols and sufficient numerical data, structural parameters were not included in the quantitative meta-analysis and were assessed descriptively.

Table 5 is descriptive in nature and reflects general differences between autologous and allogeneic MSCs; it does not represent the results of a direct quantitative comparison of efficacy.

Discussion

The results of this systematic review and meta-analysis indicate that intra-articular administration of MSCs is associated with a statistically significant reduction in pain and improvement in functional status in patients with knee osteoarthritis. Only

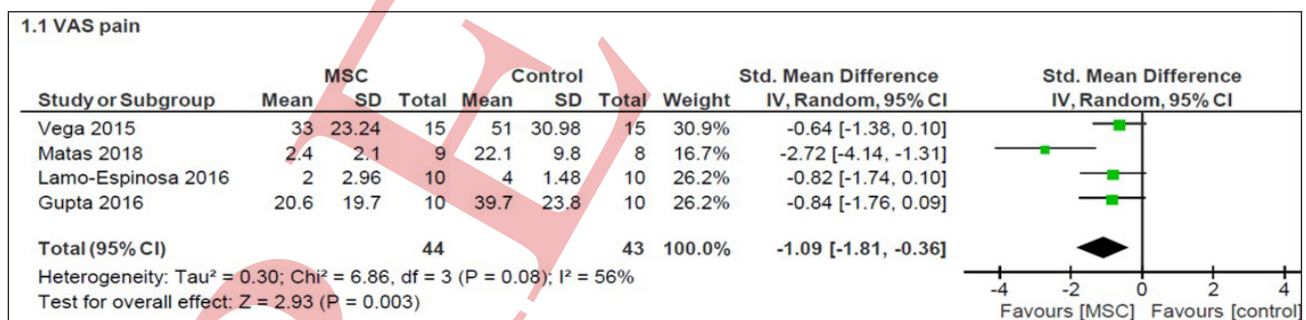


Fig. 2. Forest plot of the efficacy of MSC therapy according to the VAS

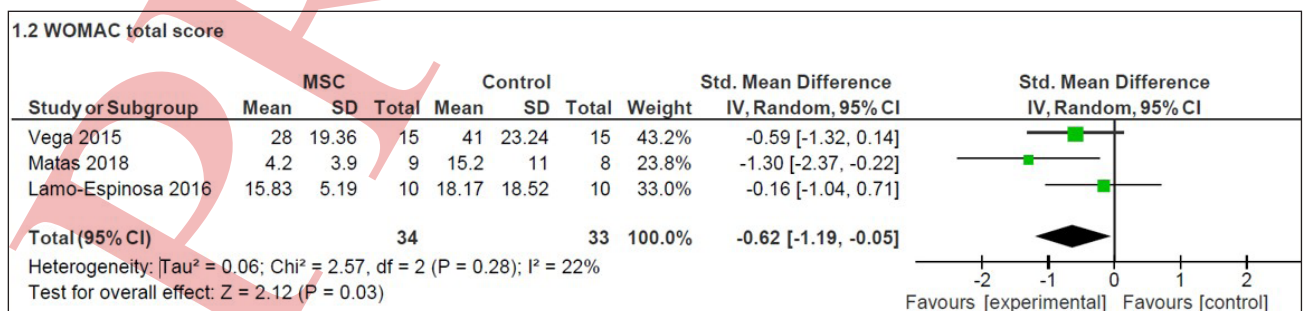


Fig. 3. Forest plot of the efficacy of MSC therapy according to the WOMAC

controlled studies with sufficient numerical data were included in the quantitative analysis, allowing a standardized comparison of the efficacy of MSC therapy with control interventions.

The VAS demonstrated a statistically significant reduction in pain in favor of MSC therapy: SMD = -1.09 ; 95 % CI: -1.81 to -0.36 ; $p = 0.003$. At the same time, heterogeneity was moderately high ($I^2 = 56\%$), which may be related to differences between studies in terms of cell source, type of control intervention, dosage, methods of cell-product preparation, and study design. Thus, the observed effect indicates the clinical potential of MSC therapy for pain reduction; however, it should be interpreted cautiously, taking into account the heterogeneity across studies.

The WOMAC also demonstrated a statistically significant improvement in functional status in favor of MSC therapy: SMD = -0.62 ; 95 % CI: -1.19 to -0.05 ; $p = 0.03$. Heterogeneity for this outcome was low ($I^2 = 22\%$), indicating relatively consistent re-

sults across the included publications. This suggests that the beneficial effects of MSC therapy may extend beyond pain reduction to improved functional capacity of the knee joint.

Analysis of the pooled data (Table 3) showed that both types of MSCs provide statistically and clinically significant reductions in pain and significant improvements in knee joint function.

These findings are consistent with the observations reported by C. H. Jo et al. [2], who demonstrated significant improvements in pain and functional outcomes in patients following intra-articular administration of autologous MSCs for post-traumatic knee joint injury. Similar effects of allogeneic cells have been reported in randomized studies by A. Vega, P. K. Gupta et al. [4, 6], in which WOMAC scores decreased by more than 35–40% over the 12-month follow-up period.

It is important to note that the quantitative meta-analysis in this study evaluated the efficacy

Table 3

Summary of the meta-analysis results

Indicator	Number of studies	Number of participants	Model	SMD [95 % CI]	I^2 , %	p	Interpretation
VAS	4	87	Random effects	-1.09 [-1.81 ; -0.36]	56	0,003	Statistically significant reduction in pain in favor of MSCs
WOMAC	3	67		-0.62 [-1.19 ; -0.05]	22	0,03	Statistically significant improvement in functional status in favor of MSCs

Table 4

Comparison of the safety of autologous and allogeneic MSCs

Parameter	Локальний біль/набряк	Інфекційне ускладнення	Імунна реакція	Серйозна побічна реакція*	Відміна лікування
Autologous MSCs	Frequent, short-term	Singular	Not registered	Not registered	NO
Allogeneic MSCs			Singular, mild		

Note. * — Severe allergic or anaphylactic reaction, septic arthritis following intra-articular administration, systemic infection, severe immune reaction requiring hospitalization, or prolonged significant deterioration of joint function.

Table 5

Comparative characteristics of autologous and allogeneic MSCs in osteoarthritis

Criterion	Аутологічні МСК	Алогенні МСК
Cell source	Patient's own tissues (bone marrow, adipose tissue)	Donor tissues (umbilical cord tissue, placenta, bone marrow)
Immunogenicity	Minimal	Low, but potentially present
Product standardization	Lower; depends on the patient's age, comorbidities, and cell quality	Higher; pre-testing and standardization of the cell product are possible
Invasiveness	Requires tissue harvesting	Does not require tissue harvesting
Clinical effect	Improvement in pain and function in selected clinical studies	Improvement in pain and function in selected clinical studies
Availability	Limited	High ("off-the-shelf")
Safety	High	High

of MSC therapy compared with control interventions rather than directly statistically comparing autologous and allogeneic MSCs with each other. Therefore, conclusions regarding the superiority of one cell type over the other are descriptive in nature.

Autologous MSCs have the advantage of biological compatibility and a minimal risk of an immune response; however, the quality of the cellular material may depend on the patient's age, comorbidities, and metabolic status. Allogeneic MSCs, in turn, offer potential advantages in terms of standardization, availability, and the possibility of using an off-the-shelf cell product; however, their long-term immunological safety requires further investigation.

The findings obtained are consistent with the biological mechanisms of action of MSCs. Their clinical effect is likely related not only to their potential chondrogenic differentiation but, primarily, to their paracrine, anti-inflammatory, and immunomodulatory activity. MSCs may influence the local joint microenvironment, reduce the activity of inflammatory mediators, and support tissue remodeling processes, which is relevant in the setting of degenerative cartilage changes.

MRI data in the included studies were assessed descriptively because the imaging techniques, assessment scales, and time points were heterogeneous. Several publications reported stabilization or moderate improvement in the structural characteristics of articular cartilage following MSC therapy. Studies by A. Vega and J. Freitag et al. [6, 10] demonstrated increased cartilage thickness and improved cartilage signal intensity according to MOCART-like scales, which is particularly relevant in patients with localized post-traumatic defects. However, the available data are insufficient for a quantitative meta-analysis of MRI parameters; therefore, the structural effect of MSCs should be regarded as a promising but not yet sufficiently standardized area of assessment.

The safety profile of MSC therapy in the included studies was generally favorable. The most frequently reported adverse events were transient local pain, swelling, or transient synovitis following intra-articular administration. Serious adverse events, including septic arthritis, severe systemic infections, anaphylactic reactions, or clinically significant immune complications, were not reported in most studies. However, the small sample sizes and limited follow-up periods do not allow the long-term safety of the therapy to be assessed conclusively, particularly for allogeneic cell products.

From a clinical perspective, the available data suggest that MSC therapy may be considered a prom-

ising biological approach for patients with knee osteoarthritis, particularly when standard conservative treatments have limited efficacy. However, due to heterogeneity in treatment protocols, differences in cell sources, variability in dosing, and the lack of standardized criteria for assessing outcomes, MSC therapy cannot yet be considered a fully standardized treatment method.

Thus, the findings of this systematic review and meta-analysis support the potential efficacy of intra-articular MSC administration in reducing pain and improving functional status in patients with knee osteoarthritis. At the same time, the limited number of studies included in the quantitative synthesis does not allow definitive conclusions to be drawn regarding the superiority of autologous or allogeneic MSCs. Further multicenter randomized controlled trials with standardized protocols, standardized doses, clearly defined patient inclusion criteria, and long-term follow-up are needed.

Study Limitations

A number of limitations of this systematic review and meta-analysis should be noted. First, the number of studies included in the quantitative analysis was limited: 4 controlled studies for the VAS and 3 for the WOMAC. This reduces the statistical power of the analysis and limits the possibility of conducting a comprehensive subgroup analysis by MSC type.

Second, the included studies were characterized by clinical and methodological heterogeneity. The differences concerned the source of the cellular material, MSC type and dose, methods of cell preparation, control intervention, severity of osteoarthritis, duration of follow-up, and clinical scales used.

Third, not all studies reported their results in a format suitable for quantitative analysis. Some data were presented graphically, while others were reported as medians and interquartile ranges, requiring conversion to mean $\pm$ SD. This may have affected the accuracy of the calculations.

Fourth, structural changes assessed by MRI were evaluated using heterogeneous protocols and scales; therefore, these outcomes were not included in the quantitative meta-analysis and were assessed descriptively.

It should also be taken into account that a direct quantitative comparison of autologous and allogeneic MSCs was not performed in this analysis because of the insufficient number of sufficiently homogeneous studies in the respective subgroups. Therefore, conclusions regarding differences between these cell types are predominantly descriptive in nature.

Conclusions

Intra-articular administration of MSCs is associated with a statistically significant reduction in pain in patients with knee osteoarthritis. The VAS meta-analysis demonstrated a benefit of MSC therapy compared with control: SMD = -1.09; 95 % CI: -1.81 to -0.36; $p = 0.003$; $I^2 = 56\%$.

MSC therapy also demonstrated a statistically significant improvement in functional status according to the WOMAC. The pooled effect estimate from the meta-analysis was: SMD = -0.62; 95 % CI: -1.19 to -0.05; $p = 0.03$; $I^2 = 22\%$.

The safety profile of intra-articular MSC administration in the included studies was generally favorable. The most frequently reported adverse events were transient local pain, swelling, or transient synovitis following injection; most studies did not report serious adverse reactions.

The available data do not allow definitive conclusions regarding the superiority of autologous or allogeneic MSCs, as direct quantitative comparisons between these approaches were limited by the insufficient number of sufficiently homogeneous studies.

Further multicenter randomized controlled trials with standardized protocols, standardized cell doses, long-term follow-up, and uniform clinical and MRI assessment criteria are needed to determine the optimal MSC type, indications for therapy, and long-term treatment efficacy.

Conflict of Interest. The authors declare no conflict of interest.

Prospects for Further Research. Further studies should focus on multicenter randomized controlled trials involving larger patient populations and longer follow-up periods. Studies directly comparing autologous and allogeneic MSCs using the same efficacy and safety criteria are of particular importance.

A promising area of research is the standardization of cell therapy protocols, including the source of MSCs, cell preparation methods, the number of cells administered, the frequency of injections, and patient selection criteria. This would help reduce methodological heterogeneity and improve the comparability of results across studies.

Particular attention should be paid to standardized MRI assessment of structural changes in the articular cartilage and subchondral bone. The use of standardized imaging protocols and assessment scales will help determine more accurately whether the clinical improvement observed after MSC therapy is accompanied by actual structural changes in the joint tissues.

Another promising area is the investigation of predictors of response to MSC therapy, including patient age, osteoarthritis severity, body mass index, metabolic status, comorbidities, and characteristics of the cell product. This may help identify patient groups that are most likely to benefit from autologous or allogeneic cell therapy.

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INTRA-ARTICULAR ADMINISTRATION OF AUTOLOGOUS AND ALLOGENEIC MESENCHYMAL STROMAL CELLS FOR KNEE OSTEOARTHRITIS: A SYSTEMATIC REVIEW AND META-ANALYSIS OF CLINICAL STUDIES

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