DIGEST AND REVIEWS

УДК 616.71-018.3:616.728]-003.93-089*BioCartilage(048.8)

DOI: http://dx.doi.org/10.15674/0030-598720223-4126-137

Surgical techniques for the articular cartilage repair: literature review and meta-analysis

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Objective. To evaluate the clinical efficacy and safety of implementing the extracellular matrix (ECM), Autologous Matrix Induced Chondrogenesis (AMIC), adipose tissue derived mesenchymal stem cell (AD-MSCs), as well as bone marrow mesenchymal stem cells (BM-MSCs) for treating the osteochondral defects of knee joint and the talocrural one. Methods. Investigating by the facilities of PubMed, Embase and the manual searches, implemented from 2018 till January, 2022. There have been included articles with the I–IV level of evidence, studying the osteochondral defects over 0.5 cm², with at least one-year duration of monitoring more than 10 patients, defining the scores on VAS (Visual Analogue Scale), Tegner Activity Scale, FAOS (Foot and Ankle Outcome Score). The results were evaluated after 1–2, 3–5 and over 5 years-period of monitoring. Meta-analysis was applied by the facilities of RStudio. Results. 14 investigations with 720 patients were incorporated. ECM, AMIC, AD-MSCs and BM-MSCs represented significantly better functional outcomes in comparison with the bone marrow stimulation procedures (MSP) on the VAS, Tegner Activity Scale, and FAOS scales. Patients treated according to the AMIC+BMAC (bone marrow aspirate concentrate) method showed better functional results compared to the standard AMIC technique. The rate of unsuccessful manipulations followed by revision operations in the MSP group is significantly higher than in others after 4 or more years of monitoring. The results obtained in a long-term investigation showed no deterioration after 5 years or more. Conclusions. Modern methods of cartilage repair in comparison with the creation of microfractures and microdrilling provide better quality regeneration, better long-term results, fewer complications, and higher rates of return to activity. Future studies should be longer-lasting and include more representative populations to determine the efficacy and safety of these methods.

Мета. Оцінити клінічну ефективність і безпечність застосування позаклітинного матриксу (extracellular matrix, ECM), аутологічного матриксу індукції хондрогенезу (Autologous Matrix Induced Chondrogenesis, AMIC), мезенхімальних стромальних клітин жирової тканини (adipose tissue derived mesenchymal stem cell, AD-MSCs) та мезенхімальних стромальних клітин кісткового мозку (bone marrow mesenchymal stem cells, BM-MSCs) для лікування остеохондральних дефектів колінного та надп'ятково-гомілкового суглобів. Методи. Пошук у PubMed, Embase та ручний проведені із 2018 року до січня 2022. Включено статті з рівнем доказовості I–IV, вивченням остеохондральних дефектів понад 0,5 см², тривалістю спостереження за понад 10 пацієнтами не менше року, визначенням балів за VAS (Visual Analogue Scale), Tegner Activity Scale, FAOS (Foot and Ankle Outcome Score). Результати оцінювали через 1–2, 3–5 та понад 5 років спостереження. Метааналіз проведений за допомогою RStudio. Результати. Включено 14 досліджень із 720 пацієнтами. ECM, AMIC, AD-MSCs та BM-MSCs показали значно кращі результати порівняно з процедурами стимуляції кісткового мозку (marrow stimulation procedures, MSP) за шкалами VAS, Tegner Activity Scale, FAOS. У пацієнтів, які отримали лікування за методикою AMIC + BMAC визначено кращі функціональні результати порівняно зі стандартною методикою AMIC. Рівень невдалих маніпуляцій із подальшим проведенням ревізійних операцій у групі MSP значно вищий, ніж в інших через 4 та більше років спостереження. Отримані в довгостроковому дослідженні результати не показали жодних погіршень через 5 та більше років. Висновки. Сучасні методи відновлення хряща в порівнянні зі створенням мікропереломів і мікросвердленням забезпечують якіснішій регенерат, кращі довгострокові результати, мають меншу кількість ускладнень і вищі показники повернення до активності. Майбутні дослідження мають бути тривалішими й охоплювати більш репрезентативні популяції для визначення ефективності та безпеки цих методів.

Ключові слова. Остеохондральні дефекти, позаклітинний матрикс, аутологічний матрикс для індукції хондрогенезу, мезенхімальні стромальні клітини жирової тканини, мезенхімальні стромальні клітини кісткового мозку, метааналіз.

Key words. Osteochondral defects, extracellular matrix, Autologous Matrix Induced Chondrogenesis, adipose tissue derived mesenchymal stem cell, bone marrow mesenchymal stem cells, meta-analysis

Introduction

Articular cartilage is a connective tissue with a unique structure that has shock-absorbing properties, considerable durability, and the smoothness of the articular surfaces minimizes friction during movements [1]. It also has an alymphatic and hypocellular structure, which, in combination with weak metabolic activity, limits regeneration [2].

Cartilage regeneration occurs with the formation of fibrous tissue, which contains type I collagen [3, 4], significantly affecting its biomechanics [5]. Bone marrow stimulation procedure (MSP) is indicated for patients with small area (less than 150 mm^2) or diameter (less than 15 mm) defects with a depth of less than 7 mm [6, 7]. One of the cartilage repair techniques is microfracture (MFx). The main problems of this technique are the quality of the obtained reparative tissue (fibrous cartilage), the unpredictable volume of the regenerate. An alternative technique is tunneling or micro-drilling (MD). In the case of creating microfractures of the bone with the help of an awl, unlike microdrilling, the bone is compacted. Besides, more type II collagen is formed and the defect is more evenly filled [8].

«BioCartilage» is an extracellular auto- or allocartilage matrix (ECM), which contains growth factors, proteoglycans, and type II collagen [6]. The principle of its application involves creating a matrix over the defect after microfractures or microdrilling, which ensures the interaction of autologous articular cartilage cells in the regenerate. ECM requires hydration with platelet-rich plasma (PRP) or bone marrow aspirate concentrate (BMAC).

The results of the use of autologous matrix for induction of chondrogenesis (Autologous Matrix-Induced Chondrogenesis, AMIC) were published in 2005 [9]. As a result of the microfracture manipulation, a «super clot» is formed, which contains stem cells and growth factors. Consequently, it is fixed with a membrane based on porcine collagen type I/ III, thereby providing stability and favorable conditions for the formation of new cartilage tissue [10]. Matrix-associated stem cell transplantation (MAST) is a technique in which bone marrow aspirate is additionally used during AMIC [11].

Mesenchymal stromal cells (MSCs) are widely used in regenerative medicine, as they can differentiate into osteocytes and chondrocytes *in vitro* [12], for cartilage regeneration most often — mesenchymal stem cells of adipose tissue (AD-MSCs) and bone marrow (BM-MSCs) [13].

The purpose of the study: to conduct a meta-analysis and evaluate the clinical effectiveness and safety of the use of ECM, AMIC, AD-MSCs and BM-MSCs for the treatment of osteochondral defects of the knee and talocrural joints.

Material and methods

Literature search strategy

The review was prepared in accordance with the recommendations of the «Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines». PubMed and Embase were searched from 2018 to January 2022 using the following terms: «Osteochondral», «BioCartilage», «Allograft cartilage extracellular matrix», «Autologous Matrix Induced Chondrogenesis» or «AMIC», «MSC» or «Mesenchymal stem cells», «AD-MSCs», «BM-MSCs». References of reviews and studies were also manually searched.

Inclusion criteria

Studies were selected by two reviewers independently. Relevant articles were included after reading the full text and determining the necessary parameters. Inclusion criteria: 1) osteochondral defects over 0.5 cm2; 2) articles with evidence level I–IV; 3) duration of observation not less than one year; 4) more than 10 patients included in the study; 5) articles in foreign languages.

Data extraction

According to the specified criteria, two independent researchers checked the search results by title, abstract and full text. Extracted data included: first author, year of publication, level of evidence, study design, location of lesion, number and age of patients, bone marrow stimulation technique, defect size, treatment groups, primary outcomes, and follow-up. VAS (Visual Analogue Scale), Tegner Activity Scale, FAOS (Foot and Ankle Outcome Score) scores were determined. The results were evaluated after 1–2; 3–5 and more than 5 years.

Statistical analysis

Meta-analysis was performed using RStudio software (https://www.rstudio.com/), a meta package to generate hazard ratios for categorical outcomes, mean differences for continuous outcomes, and 95 % confidence intervals (CIs).

Results and their discussion

Literature search results

In total, 1,563 articles were found by searching the literature in electronic databases, of which 724 were from the PubMed database, 834 from Embase, and 5 were selected by manual search.

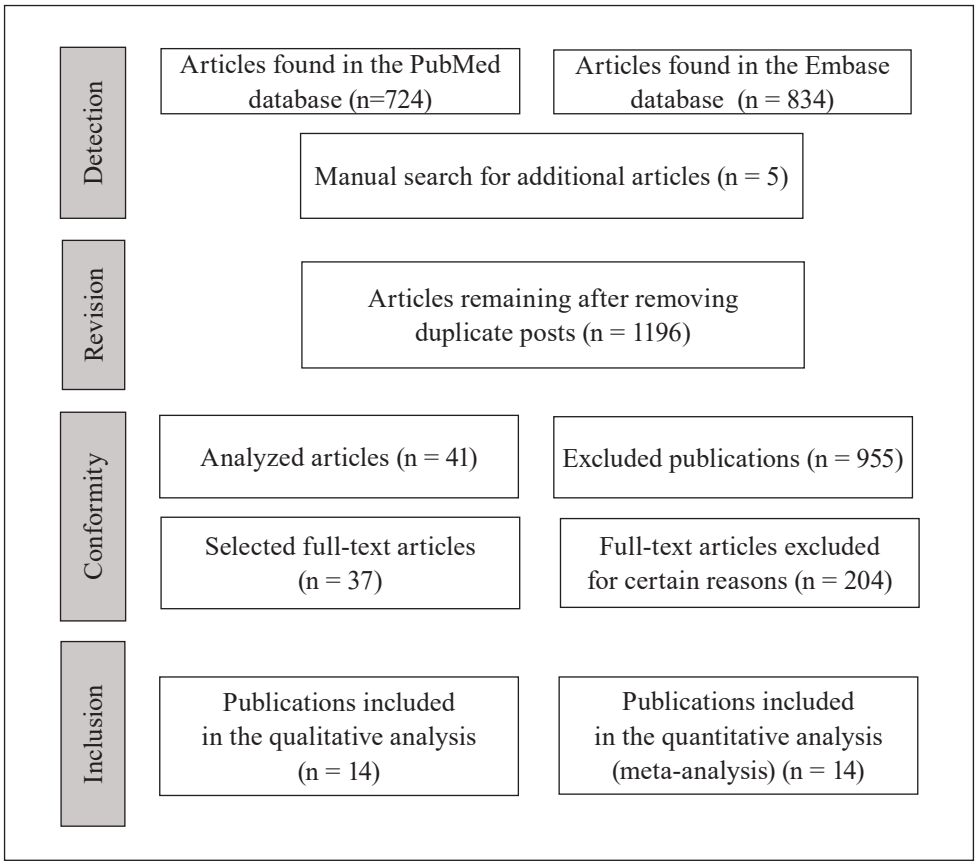


Fig. 1. Scheme of article selection for the study

Table 1

Studies included in the literature review

Author, year, country Localization of the defect (joint)	Level of evidence	Study design	Localization of the defect (joint)	Evaluation of results
Cole B. J. et al., 2021, USA [14]	III	Prospective, multi-centered, cohort	Knee	VASS
Drakos M. C. et al., 2021, USA [15]	III	Retrospective, comparative	Talocrural	FAOS
Hansen O. B. et al., 2021, USA [16]	III	Retrospective, comparative	Talocrural	FAOS
Allahabadi S. et al., 2021, USA [17]	IV	Retrospective, case series	Talocrural	VAS
De Girolamo L. et al., 2019, Italy [18]	II	Randomized, controlled	Knee	VAS, Tegner
Schagemann J. et al., 2018, Germany [19]	III	Randomized	Knee	VAS
Kaiser N. et al., 2020, Switzerland [20]	IV	Randomized	Knee	VAS
Becher C. et al., 2018, Germany [21]	III	Retrospective comparative	Talocrural	VAS
Hoburg A. et al., 2018, Germany [22]	IV	Randomized	Knee	Tegner
Migliorini F. et al., 2021, Germany a [23]	II	Prospective cohort	Talocrural	VAS, Tegner
Migliorini F. et al., 2021, Germany b [24]	II	Prospective cohort	Knee	VAS, Tegner
Murphy E. P. et al., 2019, Ireland [25]	IV	Prospective cohort	Talocrural	VAS, FAOS
Mardones R. et al., 2020, Italy [26]	IV	Retrospective	Knee	VAS
Lu L. et al., 2019, China [27]	Ib	Prospective, randomized, double blind, active controlled clinical, phase IIb	Knee	VAS

Thirty-seven potentially eligible articles were assessed by reading. Ultimately, 14 articles were included (Fig. 1).

Demographic indicators

In total, based on the materials of the selected articles, 720 patients aged 26 to 59 years were included in the study. There were 370 men among them, although it should be noted that in one study the gender distribution of patients was not reported. The duration of observation was from 12 months to 9 years. 57.14 % of cases involved the knee joint and 42.86 % the talocrural one (Tables 1, 2).

Clinical research results

Since the treatment of patients implied the use of various techniques, the surgical treatment strategies and postoperative results differed (Table 3).

Results of statistical analysis according to VAS

In 1–2 years, the mean difference for the ECM group between preoperative and postoperative results was: 2.30 (CI [1.67, 2.93]), AMIC: 4.10 (CI [2.29, 5.92]). Mean difference between AMICs and controls: -0.45 (CI [-1.01, -0.11]), AD-MSCs/BM-MSCs: -1.54 (CI [-2.51, -0, 57]). In 3–5 years, the mean difference between ECM and controls: 2.20 (CI [0.84, 3.56]), AMIC: -0.79 (CI [-1.54, -0.04]). The mean difference in the AMIC group between preoperative and postoperative results was 4.87 (CI [4.87, 5.64]), AD-MSCs/BM-MSCs — 4.00 (CI [2.95, 5.05]). For a follow-up period of more than 5 years, the average difference between AMIC and the control group was determined to be -1.17 (CI [-2.49; 0.16]), and 3.90 (CI [2.89; 4, 54]) between preoperative and postoperative indicators (Tables 4, 5).

Results of statistical analysis according to Tegner

In 1–2 years, the mean difference in AMIC between experimental and control groups was -0.73 (CI [-1.90; 0.44]), 1.44 (CI [0.99; 1.88]) in 3–5 years, and 1.11 (CI [0.70; 1.52]) for the duration of observation over 5 years (Table 4).

Results of statistical analysis according to FAOS

In 1–2 years, the difference between ECM and the control group was -3.50 (CI [-12.45, 5.45]), and 1.65 (CI [-7.15, 10, 45]) in 3-5 years (Table 5).

Complications

No intraoperative complications were reported. Among 14 studies (with the participation of 720 patients), postoperative complications were not recorded in 3, and revision operations were reported in 6. They were performed due to constant pain syndrome, progression of degenerative changes in the joint, unsuccessful surgical intervention.

Discussion

ECM showed significantly better VAS outcomes at 3–5 years of follow-up compared to MFx, and MFx revealed significantly worse outcomes compared to AD-MSCs, BM-MSCs, and AMICs. According to the Tegner scale, in the case of using AMIC + BMAC under observation conditions of more than 5 years, better results were established compared to AMIC without stem cells. Regarding the FAOS score, the results of the ECM group were better at 5-year follow-up compared to MFx.

ECM is a modern, simple surgical procedure that complements the well-known MFx technique. Histological and immunohistochemical studies showed that the formed regenerate contained type II collagen. In 2021, J. Commins et al. [28] published the findings that BioCartilage acts as a scaffold and also has a characteristic composition to support cell adhesion and migration.

Better functional results were determined in patients who received treatment using the AMIC + BMAC method compared to the standard AMIC method. MRI analysis in 12 months confirmed this observation.

Comparison of the results of both groups revealed that the majority of mesenchymal progenitor cells were important in the initial stages of cartilage repair, as they accelerated the repair process. It has been demonstrated in vitro that bone marrow mesenchymal cells can differentiate into different cell types under the influence of appropriate stimuli, such as 3D culture media [29]. Significant differences between the standard AMIC procedure and AMIC + BMAC were found after one year, which may indicate that MSCs have a temporary effect on the repair processes, reducing the local inflammatory process and, in turn, alleviating pain. In 2017, a group of authors published the results of a five-year study comparing the use of AMIC and MFx. Significantly better results (according to the Cincinnati, ICRS and VAS scales) were obtained after using the AMIC technology, and MRI showed more complete filling of the chondral defect [30].

The effectiveness of the use of mesenchymal stem cells for OA has been confirmed in experimental studies [31]. L. Zhou et al. in 2019 [13] conducted a meta-analysis and showed a better therapeutic effect of AD-MSCs compared to BM-MSCs, similar results were obtained later [32]. This is probably due to the stronger immunosuppressive capacity of AD-MSCs [33]; higher expression of genes responsible for binding to proteins, growth factors, or cytokine activity in extracellular compartments; less dependence on mitochondrial respiration for energy production [13]. We did not have the opportunity to fully analyze such results due to the limited number of studies in this group.

Table 2

Characteristics of publications on the treatment of osteochondral defects

Author, year, country	Patient		MSP	Defect size		Treatment	Observation period (months)
	n, gender m/f	Age (years)					
Cole B. J. et al., 2021, USA [14]	48, 37/11	31.6 ± 10.5	MFx	Area (2.4 ± 1.4) cm^2; depth (3.6 ± 3.4) mm		ECM	24
Drakos M. C. et al., 2021, USA [15]	166, 85/81	ECM + BMAC: 36.0; MFx/MFx + BMAC: 37.27	MFx	ECM + BMAC: 0.76 (0.12–2.25) cm^2; MFx/MFx + BMAC: 0.2 (0.08–2.25) cm^2		ECM + BMAC; MFx/MFx + BMAC	23.5 (12–40) 35.1 (6 months–9.5 years)
Hansen O. B. et al., 2021, USA [16]	52, 22/30	OAT: 37.7 ± 14.8; DEB: 34.6 ± 12.6	MFx	OAT: (1.21 ± 0.23) cm^2; DEB: (1.14 ± 0.23) cm^2		OAT + ECM – BMAC; MFx + DEB	DEB: 22.2 ± 7.1 OAT: 28.8 ± 11.6
Allahabadi S. et al., 2021, USA [17]	48, 23/25	MCM: 35.0 ± 13.8; MFx: 35.9 ± 16.5	MFx	MFx + MCM + BMAC/PRP: (0.64 ± 0.49) cm^2; MFx: (0.57 ± 0.44) cm^2		MFx + MCM + BMAC/PRP; MFx	4.0 ± 3.4
De Girolamo L. et al., 2019, Italy [18]	24, 15/9	34	MFx	AMIC: (3.8 ± 1.0) cm^2; AMIC +: (3.4 ± 0.8) cm^2		AMIC; AMIC + (+BMAC)	100
Schagemann J. et al., 2018, Germany [19]	50, 30/20	Arthroscopically AMIC: 38.2 ±16.3; Mini-arthrotomy + AMIC: 34.4 ± 11.3	MFx	Arthroscopically AMIC: (3.1 ± 1.4) cm^2; Mini-arthrotomy + AMIC: (3.4 ± 2.4) cm^2		AMIC: Arthroscopically; Mini-arthrotomy	24
Kaiser N. et al., 2020, Switzerland [20]	33, 22/11	37.1 ± 11.9	MD	(2.8 ± 1.6) cm^2		AMIC	(9.3 ± 1.0) years
Becher C. et al., 2018, Germany [21]	32, 14/18	AMIC: 32.4 ± 12.5 MFx: 33.3 ± 9.3	MFx	< 2 m^2		AMIC; MFx	AMIC: (5.7 ± 0.7) years MFx: (5.6 ± 0.5) years
Hoburg A. et al., 2018, Germany [22]	15, 9/6	26	MD	(4.98 ± 3.02) cm^2		AMIC	49 (36 – 61)
Migliorini F. et al., 2021, Germany a [23]	70, 39/31	AMIC: 31.5 ± 2.1 MFx: 33.3 ± 6.2	MFx	2.7 cm^2		AMIC; MFx	43.5
Migliorini F. et al., 2021, Germany b [24]	83, 46/28	AMIC: 29.5 ± 12.1 MFx: 31.3 ± 9.9	MFx	AMIC: (2.8 ± 2.5) cm^2; MFx: (2.6 ± 1.8) cm^2		AMIC; MFx	AMIC: 43.7 ± 27.6 MFx: 39.5 ± 19.1
Murphy E. P. et al., 2019, Ireland [25]	32, 22/10	35	MFx	> 1.5 cm^2		MAST	36.7 (12 – 64)
Mardones R. et al., 2020, Italy [26]	15, -/-	35.8	MFx	2.0 × 1.7 (1.5 × 1.0 – 3.0 × 3.0) cm		BM-MSCs	32 (12 – 46)
Lu L. et al., 2019, China [27]	52, 6/46	AD-MSCs: 55.03 ± 9.19 HA: 59.64 ± 5.97	MFx	Volume of the lesion according to MRI (mm^3)		AD-MSCs; HA	12
				AD-MSCs: Left knee joint 9.54 (0.19) Right — 9.54 (0.18)	HA: Left knee joint 9.62 (0.19) Right — 9.59 (0.19)		

Note. MFx — microfractures; ECM - extracellular matrix; BMAC — bone marrow aspirate concentrate; OAT — osteochondral autograft transplantation; DEB — debridement with ECM-BMAC (a combination of extracellular matrix and bone marrow aspirate concentrate); MCM — micronized cartilage matrix; PRP — platelet-rich plasma; AMIC — autologous matrix-induced chondrogenesis; MD — microdrilling; MAST — matrix-associated stem cell transplantation; BM-MSCs — bone marrow mesenchymal stromal cells; AD-MSCs — mesenchymal stromal cells of adipose tissue; HA - hyaluronic acid.

Table 3

Results of surgical treatment of osteochondral defects

Author, year, country	Operation outcome	
Cole B. J. et al., 2021, USA [14]	VAS score: in 1 year — 1.4 ± 1.7 in 2 years — 1.4 ± 1.9	
Drakos M. C. et al., 2021, USA [15]	FAOS score: ECM + BMAC — 69.32 ± 21.63; MFx/MFx + BMAC — 67.67 ± 23.10	
Hansen O. B. et al., 2021, USA [16]	FAOS score: – pain in OAT 86.7 ± 14.3; in DEB — 81.5 ± 17.3 – symptoms in OAT 80.1 ± 13.8; DEB — 75.2 ± 18.2 – daily activity in OAT 92.8 ± 8.7; DEB — 91.1 ± 12.2 – sport activity in OAT 70.6 ± 24.9; DEB —73.3 ± 26.1 – life quality in OAT 64.1 ± 25.4; DEB — 59.8 ± 26.6 – total in OAT 79.7 ± 15.2; DEB — 76.2 ± 17.7	
Allahabadi S. et al., 2021, USA [17]	Difference between initial and final VAS scores	
	MCM + BMAC/PRP 6 weeks — 3.6 ± 2.2 3 months — 3.7 ± 2.6 6 months — 4.2 ± 2.8 Final — 4.9 ± 2.2	MFx 6 weeks — 3.3 ± 1.7 3 months — 2.8 ± 2, 6 months — 1.9 ± 2.5 Final — 2.7 ± 2.6
De Girolamo L. et al., 2019, Italy [18]	**VAS:** AMIC 6 months — 3.3 ± 1.8 (0–7) (n=12) 12 months — 3.0 ± 1.8 (0–6) (n=11) 24 months — 0.8 ± 0.9 (0–2) (n=11) 60 months 0.9 ± 1.4 (0–4) (n=10) 100 months — 2.7 ± 2.8 (0–8) (n=7) AMIC + 6 months — 1.9 ± 1.4 (0–8) (n=11) 12 months — 1.1 ± 1.3 (0–3,5) (n=11) 24 months — 0.6 ± 0.8 (0–2) (n=10) 60 months — 1.2 ± 1.3 (0–4) (n=10) 100 months — 0.9 ± 1.1 (0–3) (n=9)	**Tegner:** AMIC 6 months — 4.5 ± 2.0 (3–9) (n=12) 12 months — 5.6 ± 1.9 (2–9) (n=11) 24 months — 6.3 ± 2.2 (3–10) (n=11) 60 months — 5.6 ± 1.4 (3–7) (n=10) 100 months — 4.9 ± 2.5 (1–8) (n=7) AMIC + 6 months — 3.6 ± 0.9 (2–5) (n=11) 12 months — 5.0 ± 1.8 (3–9) (n=11) 24 months — 5.4 ± 2.0 (2–9) (n=10) 60 months — 5.0 ± 2.2 (2–9) (n=10) 100 months — 4.7 ± 1.3 (3–7) (n=9)
Schagemann J. et al., 2018, Germany [19]	VAS score in 1 year: – arthroscopically AMIC — 2.45 ± 2,04 – mini-arthrotomy + AMIC — 2.37 ± 220 in 2 years – arthroscopically AMIC — 1.48 ± 1.5 – mini-arthrotomy + AMIC — 2.07 ± 2.42	
Kaiser N. et al., 2020, Switzerland [20]	VAS score: in 2 years — 2.0 ± 2.1 in 9 years — 1.9 ± 1.6	
Becher C. et al., 2018, Germany [21]	VAS score: AMIC — 3.3 ± 2.3 MFx — 4.1 ± 2.5	
Hoburg A. et al., 2018, Germany [22]	VAS score in: 6 months — 4.2 ± 2.2 12 months — 2.1 ± 1.9 final — 2.4 ± 2.6	Tegner score in: 6 months — 2.7 12 months — 4.0 final — 4.7
Migliorini F. et al., 2021, Germany a [23]	VAS score: AMIC — 1.9 ± 0.8 MFx — 3.3 ± 3.1	Tegner score: AMIC — 4.3 ± 1.5 MFx — 3.1 ± 2.1
Migliorini F. et al., 2021, Germany b [24]	VAS score: AMIC — 2.5 ± 2.1 MFx — 4.1 ± 3.3	Tegner score: AMIC — 4.8 ± 1.5 MFx — 3.1 ± 0.9
Murphy E. P. et al., 2019, Ireland [25]	VAS score: 3.8 (± 2.3 SE) FAOS score: – pain — 73.4 (± 18.2 SE) – ADL — 79.1 (± 18.4 SE) – symptoms — 70.7 (± 19.1 SE) – sport — 58.8 (± 27.1 SE) – QOL — 49.9 (± 29.2 SE)	

Continuation of Table 3

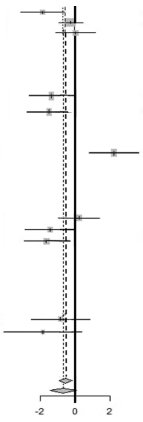
Mardones R. et al., 2020, Italy [26]	VAS score: – at rest — 0 (0–3; SD 1.09) – at work/going in for sports — 1 (0–5; SD 1.74)
Lu L. et al., 2019, China [27]	VAS score in 6 months: – AD-MSCs: left knee joint — 2.85 ± 2.65; right —3.00 ± 2.62; – HA: left knee joint — 4.17 ± 2.55; right — 4.50 ± 2.71 VAS score in 12 months: – AD-MSCs: left knee joint — 2.83 ± 2.68; right — 2.78 ± 2.58 – HA: left knee joint — 4.29 ± 2.35; right — 4.40 ± 2.43

Note. VAS — Visual Analogue Scale; FAOS — Foot and Ankle Outcome Score; ECM - extracellular matrix; AMIC — autologous matrix-induced chondrogenesis; OAT — osteochondral autograft transplantation; DEB — debridement with ECM-BMAC (a combination of extracellular matrix and bone marrow aspirate concentrate); MFx — microfractures; MCM — micronized cartilage matrix; BMAC — bone marrow aspirate concentrate; PRP — platelet-rich plasma; AD-MSCs — mesenchymal stromal cells of adipose tissue; HA - hyaluronic acid.

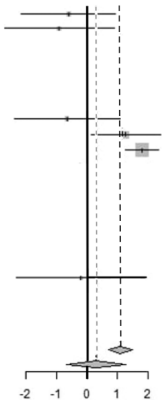
Table 4

Forest plot for comparing VAS and Tegner scores in experimental and control groups

Study of subgroup	Experimental			Control			MD	95% - CI	Weight (%)		Mean difference
	Total	Mean	SD	Total	Mean	SD			(common)	(random)	
Comparison of VAS score after 1–2 years											
1.1.1 Застосування AMIC/AMIC + BMAC											
De Girolamo L. et al., 2019, Italy [18]	11	1.10	1.30	11	3.00	1.80	-1.90	[-3.21; -0.51]	8.1	9.3	
	10	0.60	0.80	11	0.80	0.90	-0.20	[-0.93; 0.53]	26.5	11.7	
Schagemann J. et al., 2018, Germany [19]	20	2.45	2.04	30	2.37	2.20	0.08	[-1.11; 1.27]	9.9	9.8	
Common effect model	**41**			**52**			**-0.45**	**[-1.01; 0.11]**	**44.5**	—	
Random effect model							**-0.60**	**[-1.71; 0.51]**	—	**30.8**	
Heterogeneity: I^2 = 66 %; τ^2 = 0.6615, p = 0.05											
1.1.2 Application BM-MSCs/AD-MSCs											
Lu L. et al., 2019, China [27]	26	2.83	2.68	26	4.29	2.35	-1.46	[-2.83; -0.09]	7.5	9.1	
	26	2.78	2.58	26	4.40	2.43	-1.62	[-2.98; -0.26]	7.5	9.1	
Common effect model	**52**			**52**			**-1.54**	**[-2.51; -0.57]**	**15**	**—**	
Random effect model							**-1.54**	**[-2.51; -0.57]**	**—**	**18.2**	
Heterogeneity: I^2 = 0 %; τ^2 = 0, p = 0.87											
Comparison of VAS score after 3–5 years											
1.1.3 Application BioCartilage											
Allahabadi S. et al., 2021, USA [17]	20	4,90	2.20	28	2.70	2.60	2.20	[0.84; 3.56]	7.5	9.1	
Common effect model	**20**			**28**			**2.20**	**[0.84; 3.56]**	**7.5**	**—**	
Random effect model									**—**	**9.1**	
Heterogeneity: Not applicable											
1.1.4 Application AMIC/AMIC + BMAC											
de Girolamo L. et al., 2019, Italy [18]	10	1.20	1.30	10	0.90	1.40	0.30	[-0.88; 1.48]	10.0	9.8	



Continuation of Table 4

Migliorini F. et al., 2021, Germany a [23]	52	1.90	0.80	18	3.30	3.10	-1.40	[-2.85; 0.05]	6.7	8.7	
Migliorini F. et al., 2021, Germany b [24]	52	2.50	2.10	31	4.10	3.30	-1.60	[-2.89; -0.31]	8.3	9.4	
Common effect model	**114**			**59**			**-0.79**	**[-1.54; -0.04]**	**25.0**	**—**	
Random effect model							**-0.86**	**[-2.09; 0.37]**	**—**	**27.9**	
Heterogeneity: I^2 = 69 %; τ^2 = 0.7327, p = 0.07											
Comparison of VAS score after 5 and more years											
1.1.4 Application AMIC/AMIC + BMAC											
Becher C. et al., 2018, Germany [21]	16	3.30	2.30	16	4.10	2.50	-0.80	[-2.46; 0.86]	5.1	7.9	
De Girolamo L. et al., 2019, Italy [18]	9	0.90	1.10	7	2.70	2.80	-1.80	[-4.00; 0.40]	2.9	6.1	
Common effect model	**25**			**25**			**-1.17**	**[-2.49; 0.16]**	**8**	**—**	
Random effect model							**-1.17**	**[-2.49; 0.16]**	**—**	**14**	
Heterogeneity: I^2 = 0 %; τ^2 = 0, p = 0.48											
Total											
Common effect model	**252**			**214**			**-0.55**	**[-0.93; -0.18]**	**100**	**—**	
Random effect model							**-0.69**	**[-1.42; 0.05]**	**—**	**100**	
Heterogeneity: I^2 = 70 %; τ^2 = 1.0681, p = <0.01											
Comparison of Tegner score after 1–2 years											
1.3.1 Application AMIC/AMIC + BMAC											
De Girolamo L. et al., 2019, Italy [18]	11	5.00	1.80	11	5.60	1.90	-0.60	[-2.15; 0.95]	7	15,7	
	10	5.40	2.00	11	6.30	2.20	-0.90	[-2.70; 0.90]	5.1	13.8	
Common effect model	**21**			**22**			**-0.73**	**[-1.90; 0.44]**	**12.1**	**—**	
Random effect model								**[-1.90; 0.44]**	**—**	**29.5**	
Heterogeneity: I^2 = 0 %; τ^2 = 0, p = 0.80											
Comparison of Tegner score after 3–5 years											
1.3.2 Application AMIC/AMIC + BMAC											
De Girolamo L. et al., 2019, Italy [18]	10	5.00	2.20	10	5.60	1.40	-0.60	[-2.22; 1.02]	6.4	15.1	
Migliorini F. et al., 2021, Germany a [23]	52	4.30	1.50	18	3.10	2.10	1,20	[0.15; 2.25]	15.0	19.7	
Migliorini F. et al., 2021, Germany b [24]	52	4.80	1.50	31	3.10	0.90	1.70	[1.18; 2.22]	62.5	23.7	
Common effect model	**114**			**59**			**1.44**	**[0.99; 1.88]**	**83.9**		
Random effect model							**0.96**	**[-0.27; 2.18]**		**58.5**	
Heterogeneity: I^2 = 73 %; τ^2 = 0.8688, p = 0.03											
Comparison of Tegner score after 5 years and more											
1.3.3 Application AMIC/AMIC + BMAC											

Continuation of Table 4

De Girolamo L. et al., 2019, Italy [18]	9	4.70	1.30	7	4.90	2.50	-0.20	[-2.24; 1.84]			
Common effect model	**9**			**7**			**-0.20**	**[-2.24; 1.84]**	**4**	**—**	
Random effect model									**—**	**12**	
Heterogeneity: Not applicable											
Total											
Common effect model	**159**			**88**			**1.11**	**[0.70; 1.52]**	**100.0**	**—**	
Random effect model							**0.31**	**[-0.68; 1.29]**	**—**	**100.0**	
Heterogeneity: I^2 = 76 %; τ^2 = 0.007, p = < 0.01											

Note. VAS — Visual Analogue Scale; AMIC, AMIC — autologous matrix-induced chondrogenesis; BMAC — bone marrow aspirate concentrate; BM-MSCs — bone marrow mesenchymal stromal cells; AD-MSCs — mesenchymal stromal cells of adipose tissue.

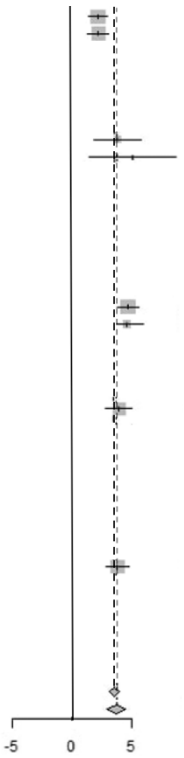
Table 5

Forest plot for comparing FAOS i VAS scores in experimental and control groups

Study of subgroup	Experimental			Control			MD	95% - CI	Weight (%)		Mean difference
	Total	Mean	SD	Total	Mean	SD			(common)	(random)	
Comparison of FAOS score after 1–2 years											
1.5.1 Application BioCartilage											
Oliver B. Hansen et al., 2021, USA [16]	27	76.20	17.70	25	79.70	15.20	-3.50	[-12.45; 5.45]	49.2	49.2	
Common effect model	**27**			**25**			**-3.50**	**[-12.45; 5.45]**	**49.2**	**—**	
Random effect model									**—**	**49.2**	
Heterogeneity: Not applicable											
Comparison of FAOS score after 3–5 years											
1.5.2 Application BioCartilage											
Drakos M. C. et al., 2021, USA [15]	40	69.32	21.63	63	67.67	23.10	1.65	[-7.15; 10.45]	50.8	50.8	
Common effect model	**40**			**63**			**1.65**	**[-7.15; 10.45]**	**50.8**	**—**	
Random effect model									**—**	**50.8**	
Heterogeneity: Not applicable											
Total											
Common effect model	**67**			**88**			**-0.88**	**[-7.16; 5.39]**	**100.0**	**—**	
Random effect model							**-0.88**	**[-7.16; 5.39]**	**—**	**100.0**	
Heterogeneity: I^2 = 0 %; τ^2 = 0, p = 0.42											
Study of subgroup	Baseline			Follow up			MD	95% - CI	Weight (%)		
	Total	Mean	SD	Total	Mean	SD			(common)	(random)	
Comparison of VAS score after 1–2 years											
2.1.1 Application BioCartilage											
Cole B. J. et al., 2021, USA [14]	49	3.70	2.60	49	1.40	1.70	2.30	[1.43; 3.17]	20.3	15.6	
	49	3.70	2.60	49	1.40	1.90	2.30	[1.40; 3.20]	18.9	15.4	

Continuation of Table 5

Common effect model	**98**			**98**			**2.30**	**[1.67; 2.93]**	**39.2**	**—**
Random effect model							**2.30**	**[1.67; 2.93]**	**—**	**31**
Heterogeneity: I^2 = 0 %; τ^2 = 0, p = 1.00										
2.1.2 Application AMIC/AMIC + BMAC										
Kaiser N. et al., 2020, Switzerland [20]	34	5.80	5.80	34	2.00	2.10	3.80	[1.73; 5.87]	3.6	8.6
Hoburg A. et al., 2018, Germany [22]	15	7.20	1.40	15	2.40	2.60	5.10	[1.33; 8.87]	1.1	3.8
Common effect model	**49**			**49**			**4.10**	**[2.29; 5.92]**	**4.7**	**—**
Random effect model							**4.10**	**[2.29; 5.92]**	**—**	**12.4**
Heterogeneity: I^2 = 0 %; τ^2 = 0, p = 0.55										
Comparison of VAS score after 3–5 years										
2.1.3 Application AMIC/AMIC + BMAC										
Murphy E. P. et al., 2019, Ireland [25]	32	8.70	1.20	32	3.80	2.30	4.90	[4.00; 5.80]	19.0	15.5
Hoburg A. et al., 2018, Germany [22]	15	7.20	1.40	15	2.40	2.60	4.80	[3.31; 6.29]	6.9	11.6
Common effect model	**47**			**47**			**4.87**	**[4.10; 5.64]**	**25.9**	**—**
Random effect model							**4.87**	**[4.10; 5.64]**	**—**	**27.1**
Heterogeneity: I^2 = 0 %; τ^2 = 0, p = 0.91										
2.1.4 Application BM-MSCs/AD-MSCs										
Mardones R. et al., 2020, Italy [26]	19	4.00	1,37	19	0.00	1.90	4.00	[2.95; 5.05]	13.9	14.5
Common effect model	**19**			**19**			**4.00**	**[2.95; 5.05]**	**13.9**	**—**
Random effect model									**—**	**14.5**
Heterogeneity: Not applicable										
Comparison of VAS score after 5 and more years										
2.1.5 Application AMIC/AMIC + BMAC										
Kaiser N. et al., 2020, Switzerland [20]	34	5.80	2.40	34	1.90	1.60	3.90	[2.89; 4.54]	16.4	15.0
Common effect model	**34**			**34**			**3.90**	**[2.89; 4.54]**	**16.4**	**—**
Random effect model									**—**	**15.0**
Heterogeneity: Not applicable										
Total										
Common effect model	**327**			**327**			**3.55**	**[3.16; 3.94]**	**100.0**	**—**
Random effect model							**3.71**	**[2.89; 4.54]**	**—**	**100.0**
Heterogeneity: I^2 = 76 %; τ^2 = 0.926, p = < 0.01										



Note. FAOS — Foot and Ankle Outcome Score; VAS — Visual Analogue Scale; AMIC — autologous matrix-induced chondrogenesis; BMAC — bone marrow aspirate concentrate; BM-MSCs — bone marrow mesenchymal stromal cells; AD-MSCs - mesenchymal stromal cells of adipose tissue.

Conclusions

Modern methods of cartilage restoration compared to MFx and MD provide better quality regenerate, better long-term results, have fewer complications and higher rates of return to activity. Future studies should last longer and include more representative populations to determine the efficacy and safety of these methods.

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

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The article has been sent to the editors 17.08.2022

SURGICAL TECHNIQUES FOR THE ARTICULAR CARTILAGE REPAIR: LITERATURE REVIEW AND META-ANALYSIS

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