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Matrix-induced chondrogenesis in the treatment of patients with osteoarthritis of the first metatarsophalangeal: a systematic review

Condrogénesis inducida por matriz en el tratamiento de pacientes con artrosis de la primera metatarsofalángica: una revisión sistemática

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ABSTRACT. Osteoarthritis of the first metatarsophalangeal joint (MTP) is a common disease of the foot and is associated with decreased range of motion, especially dorsal flexion. It is the second most common pathological condition of the foot, generating pain and stiffness. Treatment for this type of osteoarthritis is still a challenge. Autologous matrix-induced chondrogenesis (AMIC) has emerged as an alternative for treating osteoarthritis while maintaining joint mobility, which has already shown good results in other regions. AMIC has good results in chondral degeneration stages I/II, but it is impossible to assign precise indication criteria for its use. Studies are needed to evaluate advanced stages of degeneration. Good functional and clinical stability have been observed in up to five years of follow-up evaluations. Associations such as cheilectomy and/or osteotomy enhance the results. Currently, there are several different techniques for approaching MTP osteoarthritis and AMIC could be an alternative, however, there is a need for studies evaluating long-term approaches, as well as their complications.

Keywords: autologous matrix induced chondrogenesis (AMIC), chondral defect, first metatarsophalangeal joint, osteoarthritis.

RESUMEN. La artrosis de la primera articulación metatarsofalángica (MTP) es una enfermedad frecuente del pie y se asocia a una disminución de la amplitud de movimiento, especialmente de la flexión dorsal. Es la segunda afección patológica más frecuente del pie y genera dolor y rigidez. El tratamiento de este tipo de osteoartritis sigue siendo un reto. La condrogénesis inducida por matriz (AMIC) ha surgido como una alternativa para tratar la osteoartritis manteniendo la movilidad articular, que ya ha mostrado buenos resultados en otras regiones. La AMIC presenta buenos resultados en los estadios I/II de degeneración condral, pero aún no es posible asignar criterios de indicación precisos para su uso. Se necesitan estudios para evaluar los estadios avanzados de degeneración. Se ha observado una buena estabilidad funcional y clínica en evaluaciones de hasta cinco años de seguimiento. Asociaciones como la queilectomía y/o la osteotomía mejoran los resultados. Actualmente, existen diferentes técnicas para el abordaje de la artrosis de la MTP y la AMIC podría ser una alternativa, sin embargo, son necesarios estudios que evalúen los abordajes a largo plazo, así como sus complicaciones.

Palabras clave: condrogénesis inducida por matriz autóloga (AMIC), defecto condral, primera articulación metatarsofalángica, osteoartritis.

Level of evidence: II

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Abbreviations:
AMIC = autologous matrix induced chondrogenesis
AOFAS = American Orthopaedic Foot and Ankle Society
MTP = metatarsophalangeal joint
PICO = Population, Intervention, Comparison, Outcome
PRISMA = Preferred Reporting Items for Systematic reviews and Meta-Analyses
VAS = visual analog scale
VASFA = visual analog scale foot and ankle

Introduction

Osteoarthritis of the first metatarsophalangeal joint (MTP) is a disease characterized by joint pain and stiffness associated with decreased range of motion, especially dorsal flexion.[1] It is the second most common pathological condition of the foot after hallux valgus deformity, with an incidence between 2.5 and 10% of the adult population.[2]

There are currently several different surgical treatment modalities for the first MTP joint, such as cheilectomy, shortening osteotomy of the first metatarsal bone, hemiarthroplasty, endoprosthesis and arthrodesis of the first MTP joint, each of which has its advantages and disadvantages.[3,4]

Each form of treatment has its particularities, with cheilectomy and osteotomy being preferred in milder stages, while arthroplasty and arthrodesis are preferred in severe cases.[5] Matrix-induced chondrogenesis has emerged as an alternative for treating osteoarthritis while maintaining joint mobility.[6]

In addition, it is known that autologous matrix-induced chondrogenesis (AMIC) is used successfully in the presence of bone-cartilage defects in the knee, hip, and ankle, demonstrating clinical and functional improvement in patients.[7,8] In this sense, the possibility of using this treatment modality for other chondral degenerative diseases is growing.

With this in mind, this study aims to review the evidence for using matrix-induced chondrogenesis to treat first metatarsophalangeal joint osteoarthritis.

Material and methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Search strategy and selection criteria

A systematic literature search was conducted in the following databases: PubMed/MEDLINE, Embase, Cochrane and Scopus. The main health science descriptors searched in English were: «*Matrix-induced chondrogenesis*», «*Hallux Rigidus*», «*first metatarsophalangeal*». The full phrase used for the search was «Matrix-induced chondrogenesis» AND («Hallux Rigidus» OR «first metatarsophalangeal») in the databases. Initially, all studies discussing matrix-induced chondrogenesis treatment for osteoarthritis of the metatarsophalangeal joint of the first toe were approached for screening, and selected using the criteria.

The inclusion criteria were: a) studies that dealt with matrix-induced chondrogenesis of the first metatarsophalangeal joint; b) studies that used validated functional criteria for functional assessment; c) followed-up cases for at least 12 months; d) classified the stage of development of the degenerative disease.

The exclusion criteria were: a) studies that did not evaluate morphofunctional changes in humans; b) studies that carried out tests on cadavers; c) complications related to other pre-existing pathologies; d) studies that did not fully describe the treatment; e) biomechanical tests; f) case reports.

The articles were also selected according to the Population, Intervention, Comparison, Outcome (PICO) strategy.

Population: patients diagnosed with osteoarthritis of the first metatarsophalangeal joint of any degree/stage.

Intervention: functional analysis of the matrix-induced chondrogenesis treatment for a period equal to or greater than 12 months.

Comparison: by observing the evolution of the disease with the treatment modalities.

Outcome: to identify whether the matrix-induced chondrogenesis approach has similar results to other existing forms of treatment.

Functional assessment tool

Given that the aim of this study is to evaluate functional aspects based on the degree of development and treatment modality, we chose to use widely used scales, such as the American Orthopaedic Foot and Ankle Society (AOFAS) and the visual analog scale (VAS). However, due to the lack of studies, other classifications can also be used if they are validated.

Data extraction

After an initial assessment of the abstracts against the criteria, the relevant studies were selected for full reading and sorted. A research team of four independent reviewers extracted the data. Disagreements between the reviewers regarding the inclusion or exclusion of a study were resolved by consensus and, when necessary, a fifth reviewer was consulted. The variables collected included mean age, gender, follow-up time, interventions carried out, degree of deformity and the functional results obtained.

Quality assessment

To assess the quality of the studies found, the Newcastle-Ottawa scale was used. This scale evaluates eight items and scores 0-9 points in relation to the selection criteria, comparability, and outcomes of the control studies.

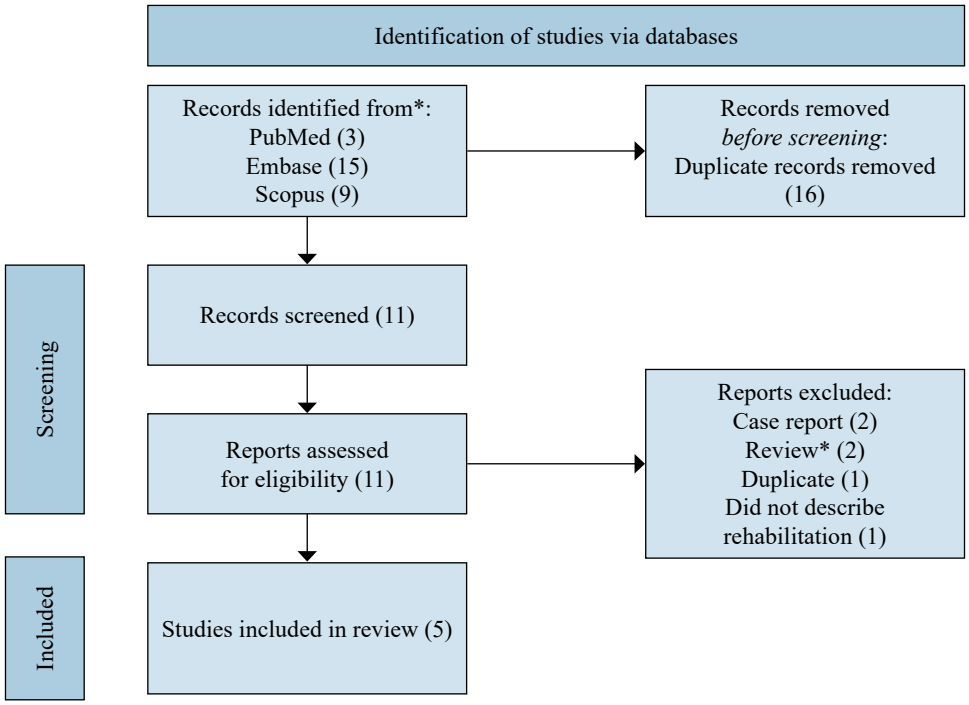

Figure 1: PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only.
* Reviews dealt with the treatment of osteoarthritis of the first metatarsophalangeal joint without addressing the AMIC technique.
Modified from: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021; 372: n71. doi: 10.1136/bmj.n71.
PRISMA = Preferred Reporting Items for Systematic reviews and Meta-Analyses.

Results

Literature search and study characteristics

A content review was carried out, first on titles and abstracts and then on full texts, which found a total of 27 articles. The 16 duplicate articles were excluded. Of these, six were excluded because they did not meet the inclusion criteria. After analysis, five articles were considered eligible *(Figure 1)*.

Characteristics of the references

The trials included a total of 383 feet and 367 patients, 16 of whom had bilateral presentations. In addition, the stage of the disease was predominantly grade two, and the average age of the studies was mostly around the fifth decade of life (48-57.6 years).

Females predominated in all the trials.

The data collected included possible risk factors for developing the disease. The analyzed results included the time of evolution, the radiographic changes' characteristics, and the procedure's performance methods. The distribution of the studies is depicted in *Table 1*.

The criteria for inclusion in the sample observed in the articles were age between 18-74 years, BMI < 40 kg/m^2, systemic inflammatory disease of medium or high activity, active infection. There was a preference for patients with unilateral involvement.

In general, AMIC showed satisfactory functional and clinical results on all the evaluation scales. Some stability was observed in the progression of the disease after treatment, and no major complications were observed in the studies. The return of range of motion was 60-70º, the scales used and their variations were VAS (1-1.5), visual analog scale for the foot and ankle (VASFA) (74.1-75), AOFAS (90-92.5), foot functional index (1-1.1) and European Society for Foot and Ankle Surgery (17.1-17.3), after a follow-up period of 12-60 months.

The complications reported were loss of amplitude reduction in one case, as well as two arthrodeses and two total replacements, among all the samples (5/383 feet).

Discussion

There are currently no well-established criteria for the precise indication of AMIC, the main relevant factor being the preservation of the metatarsophalangeal joint. None of the studies established criteria for surgical indication, and the rehabilitation protocols varied in the literature. An important factor observed in all the studies was the type of approach according to the characteristics of the injury.[6,9,10] It is notable that the main region affected is the dorsal and plantar head, usually in a single lesion.[11] Lesions of the sesamoids have also been reported.[6,9,11] Therefore, it has been established that areas of joint damage of less than 3 mm can be debrided, while multiple lesions or those

larger than 3 mm should have the entire joint surface removed.[6,9,10,11,12]

The rehabilitation protocols, although different, followed similar principles: if joint correction, such as cheilectomy and/or osteotomy, was carried out, axial overload should be avoided in the first few weeks. On the other hand, those who didn't perform a joint correction procedure could mobilize the limb earlier.[9,10] Regarding the use of orthoses in these uncorrected patients, two studies used them and two didn't, which was not reflected in the functional results of the samples.[9,11]

The association with hallux valgus was significant in the studies, in around 20% of the samples, making it important to correct the deformity in order to improve clinical results.[10]

Post-surgical X-rays showed a significant increase in joint space.[9] This phenomenon can be explained by soft tissue edema in the first few months of treatment. This change was not observed after 12 months of follow-up. Magnetic resonance imaging showed a deposit of intra-articular scar tissue in the form of a cluster, which did not affect the results.[9,11]

When assessing the stability of AMIC, there are no long-term studies currently available. However, a study conducted over five years found no worsening in functional values or increase in pain during the follow-up period.[11] One study used peripheral blood concentrates associated with AMIC to improve the adaptive process of the material.[10,11] There was no statistically significant difference found with this technique compared to the others. The matrices utilized were bovine or porcine (Aesculap Novacart Basic® and chondro-Gide®, respectively), with no preference criteria between the two, availability was the deciding factor.[9,10,11,12]

In contrast to other treatments, AMIC can be used at any stage of the degenerative disease, which can be an important factor in the decision-making process. However, studies often use combined forms with cheilectomy and associated osteotomies, which makes it a combined form of treatment.

Cheilectomy and corrective osteotomy of the first metatarsal or phalanx can yield better results in early and intermediate stages (I-II), providing reliable stabilization of the disease for up to five years.[13]

Another important factor in the studies was the degree of chondral degeneration, which was mainly intermediate (stage II), making it difficult to assess advanced stages in comparison to arthroplasty and arthrodesis of the first MTP joint. Additionally, due to the combination of treatment with cheilectomy and osteotomies, it's possible that the analysis of the results may be altered, as these two methods are preferred for mild to moderate involvement, with demonstrated functional and clinical results.[14] Therefore, it's not possible to conclude that the positive outcome was solely due to the use of AMIC.

However, the studies did not observe factors such as the reappearance of pain due to failure to repair the chondral lesion and the need for reoperation, which occur in 5-8% of cases following cheilectomy. Additionally, overload metatarsalgia, which is the main complication of shortening osteotomies,[15] was not observed. This demonstrates that AMIC can provide benefits in these cases.

The results of the studies show that when comparing AOFAS scores, metal hemiarthroplasty and arthrodesis revealed mean scores ranging from 77.3 to 94.1 and 72.8 to 91.0, respectively. Arthrodesis resulted in lower VAS pain scores (weighted mean difference -1.58, 95% confidence interval [CI] 2.16 to 1.00, $p < 0.00001$). Comparable numbers

Table 1: Characteristics of eligible studies and clinical and functional results.

Study	Year	Patients/feet	Mean age (years)	Sex male/ female	Stage	Treatment	Follow-up (months)	Outcome
Nurmukhametov MR, et al[6]	2021	19/19	48.0	4/15	3 feet/II 11 feet/III 5 feet/IV	AMIC	12	VAS (1.5) FFI (1) AOFAS (92.5) ROM (71.5º)
Richter M[10]	2021	176/176	52.6	28/148	II*	AMIC + PBC	24	VASFA (74.1) EFAS (17.1)
Nurmukhametov MR, et al[9]	2021	15/21	55.0	5/16	1 feet/I 3 feet/II 11 feet/III 6 feet/IV	AMIC	12	VAS (1) AOFAS (87.5) ROM (71.5º)
Richter M, et al[11]	2022	154/154	57.6	28/126	II*	AMIC + PBC	60	VASFA (75) EFAS (17.3)
Nurmukhametov MR, et al[12]	2020	15/16	42.2	–	I/II	AMIC	12	AOFAS (90) VASFA (9.6) ROM (67.5º) FFI (1.2)

AMIC = autologous matrix induced chondrogenesis. AOFAS = American Orthopaedic Foot and Ankle Society. EFAS = European Society for Foot and Ankle Surgery. FFI = foot functional index. ROM = range of motion. PBC = peripheral blood concentrate. VAS = visual analog scale. VASFA = visual analog scale foot and ankle.
* Studies did not classify all patients and most of them were stage II.

of complications and revisions were observed after both interventions (odds ratio 1.16, 95% CI 0.62 to 2.15, p = 0.64).[16]

Although there are no comparative studies between the methods, it is possible to indirectly evaluate the results, with AMIC showing similar and satisfactory results (AOFAS 90-92.5) at 12-60 months. In addition, it is clear from the studies that the stage of chondral disease is predominantly mild-intermediate, requiring a larger sample in stages III/IV to compare with hemiarthroplasties and arthrodeses, due to their indication being in advanced stages.

Conclusion

In this sense, given the current evidence on the use of AMIC, it is not possible to assign precise indication criteria for its use, with chondral degeneration stages I/II benefiting the most according to the characteristics of the studies. In addition, AMIC appears to be stable over a 5-year follow-up period. Techniques such as cheilectomy and osteotomy are important to guarantee a satisfactory result. With regard to the characteristics of the lesions, it is understood that areas < 3 mm can be treated only with local debridement with maintenance of healthy follow-up, while > 3 mm or multiple lesions should be treated with complete removal of the chondral tissue. There is a need to establish objective protocols for post-operative rehabilitation, as well as for indication.

Thus, AMIC has emerged as an alternative for the treatment of osteoarthritis of the first MTP joint associated with cheilectomy and/or osteotomy.

Therefore, new medium and long-term studies should be carried out, as well as comparative studies such as AMIC vs hemiarthroplasty and AMIC vs Arthrodesis in stages III/IV to better evaluate the results. Another important factor is the lack of randomized controlled studies on the subject, which in turn makes it impossible to indicate the benefits and harms of AMIC. Therefore, the choice of treatment is still surgeon-dependent and must take into account the characteristics of each patient and the cost of each procedure, with a view to clinical and functional improvement.

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