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Lateral epicondylitis treatment using mesenchymal stem cells: a narrative review

Tratamento da epicondilite lateral com células-tronco mesenquimais: uma revisão narrativa

Tratamiento de la epicondilitis lateral con células madre mesenquimales: una revisión narrativa

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Abstract
Tendons diseases are frequently seen in clinical practice, even more in athletes. This disease can be accompanied of a disabling musculoskeletal pain, being of a substantial impact in the patients' lives. Although the diverse ways to treat LE, most of the results are not satisfactory, and there is no evidence of a therapy that is more effective than placebo or no treatment at all. Therefore, throughout the last decades, new perspectives towards LE management appeared, such as mesenchymal stem cells therapy (MSCs), that demonstrated promising results in a fair number of studies. This study presents itself with the purpose to revise the existing literature towards the use of mesenchymal stem cells as a treatment to lateral epicondylitis, summarizing the existing clinical evidences and evaluating its efficacy, as to create a clear vision of the current researches and its progress in such therapy. Revise literature towards the effectiveness of stem cells use in lateral epicondylitis treatment. The review occurred in July, 2022, using original and high scientific evidence level publications in MEDLINE and Cochrane Library databases. Also, the references in which the studies were based, were also analyzed. There were selected five prospective studies that evaluated the efficacy of mesenchymal stem cells in lateral epicondylitis and other tendon diseases. All of the studies concluded that there was a significant recovery of the tendinopathy. Even though the studies show mesenchymal stem cells therapeutic potential toward lateral epicondylitis treatment, the lack o clinical trials makes it difficult to determine what type of transplant should be made, where the cells should come from and how many cells are ideal for clinical use.
Keywords: Lateral epicondylitis; Mesenchymal stem cells; Bone marrow cells.

Resumo
As doenças dos tendões são frequentemente observadas na prática clínica, ainda mais em atletas. Essa doença pode ser acompanhada de uma dor musculoesquelética incapacitante, sendo de grande impacto na vida dos pacientes. Apesar das diversas formas de tratamento do LE, a maioria dos resultados não é satisfatória, e não há evidências de uma terapia mais eficaz que o placebo ou nenhum tratamento. Assim, ao longo das últimas décadas, surgiram novas perspectivas para o manejo da LE, como a terapia com células-tronco mesenquimais (CTMs), que demonstrou resultados promissores em um bom número de estudos. Este estudo apresenta-se com o objetivo de revisar a literatura

existente sobre o uso de células-tronco mesenquimais como tratamento da epicondilite lateral, resumindo as evidências clínicas existentes e avaliando sua eficácia, de modo a criar uma visão clara das pesquisas atuais e seus avanços na tal terapia. Revisar a literatura sobre a eficácia do uso de células-tronco no tratamento da epicondilite lateral. A revisão ocorreu em julho de 2022, utilizando publicações originais e de alto nível de evidência científica nas bases de dados MEDLINE e Cochrane Library. Também foram analisadas as referências nas quais os estudos se basearam. Foram selecionados cinco estudos prospectivos que avaliaram a eficácia das células-tronco mesenquimais na epicondilite lateral e outras doenças do tendão. Todos os estudos concluíram que houve uma recuperação significativa da tendinopatia. Embora os estudos mostrem potencial terapêutico das células-tronco mesenquimais para o tratamento da epicondilite lateral, a falta de ensaios clínicos dificulta a determinação de que tipo de transplante deve ser feito, de onde as células devem vir e quantas células são ideais para uso clínico.
Palavras-chave: Cotovelo de tenista; Células-tronco mesenquimais; Células da medula óssea.

Resumen

Las enfermedades de los tendones son frecuentes en la práctica clínica, más aún en deportistas. Esta enfermedad puede acompañarse de un dolor musculoesquelético incapacitante, siendo de un impacto sustancial en la vida de los pacientes. A pesar de las diversas formas de tratar la LE, la mayoría de los resultados no son satisfactorios y no hay evidencia de una terapia que sea más efectiva que el placebo o ningún tratamiento. Por lo tanto, a lo largo de las últimas décadas, aparecieron nuevas perspectivas para el manejo de LE, como la terapia con células madre mesenquimales (MSC), que demostró resultados prometedores en un buen número de estudios. Este estudio se presenta con el propósito de revisar la literatura existente sobre el uso de células madre mesenquimales como tratamiento de la epicondilitis lateral, resumiendo las evidencias clínicas existentes y evaluando su eficacia, para crear una visión clara de las investigaciones actuales y sus avances en tal terapia. Revisar la literatura sobre la efectividad del uso de células madre en el tratamiento de la epicondilitis lateral. La revisión se realizó en julio de 2022, utilizando publicaciones originales y con alto nivel de evidencia científica en las bases de datos de MEDLINE y Cochrane Library. Asimismo, también se analizaron las referencias en las que se basaron los estudios. Se seleccionaron cinco estudios prospectivos que evaluaron la eficacia de las células madre mesenquimales en la epicondilitis lateral y otras enfermedades de los tendones. Todos los estudios concluyeron que hubo una recuperación significativa de la tendinopatía. Si bien los estudios muestran el potencial terapéutico de las células madre mesenquimales para el tratamiento de la epicondilitis lateral, la falta de ensayos clínicos dificulta determinar qué tipo de trasplante se debe realizar, de dónde deben provenir las células y cuántas células son ideales para uso clínico.
Palabras clave: Codo de tenista; Células madre mesenquimatosas; Células de la médula ósea.

1. Introduction

Tendons diseases are frequently seen in clinical practice, even more in athletes (Imam et al., 2017). Those structures are susceptible to excessive use and degeneration, but, usually, these injuries heal with fibrotic and scarring tissue, which makes these areas prone to other lesions (Young, 2012). Lateral epicondylitis (LE), also called tennis elbow, it is the most common elbow disease affecting until 3% of general population and 50% of the tennists, it is a public health problem since its high incidence in manual workers (Lee et al., 2015; Lenoir et al., 2019; Evans et al., 2019). This disease can be accompanied of a disabling musculoskeletal pain, being of a substantial impact in the patients' lives (Itro et al., 2022).

Although the diverse ways to treat LE, most of the results are not satisfactory, and there is no evidence of a therapy that is more effective than placebo or no treatment at all (Houck et al., 2019). The corticosteroids injection (CSI) is the most used therapeutic method, but its effects doesn't last long periods of time (Fujihara et al., 2018). The platelet rich plasma (PRP) and autologous blood presented themselves as more effective than CSI, but their benefit when confronted to placebo were not consistently demonstrated (Linnamnmãki et al., 2020; Branson et al., 2017). Another option to treat tennis elbow is extracorporeal shock waves therapy (ESWT), however its efficacy is controverse and its effects were, also, not distinct to placebo (Yao et al., 2020; Aydin & Atic, 2018).

Therefore, throughout the last decades, new perspectives towards LE management appeared, such as mesenchymal stem cells therapy (MSCs), that demonstrated promising results in a fair number of studies (Young, 2012; Cho et al., 2021; Van den Boom et al., 2020). The cells can be extracted from the patient itself or can be donated by other individuals, they can be found in the bone marrow and in the adipose tissue, but the adipose mesenchymal stem cells (AMSCs) are better than

mesenchymal stem cells in some aspects (Trebinjac & Gharairi, 2020; Gianakos et al., 2017). By being easily extracted through liposuction, the AMSCs present themselves with lower risk of rejection to the receiver, are stabler in cultures in the long term and are more numerous when compared to MSCs, by a number of 1 – 10% against 0,001-0,01% (Trebinjac & Gharairi, 2020; Torres-Torrillas et al., 2019).

The MSCs are able to differentiate to distinct cellular types, such as tenocytes, enhancing tendon repair (Itro et al., 2022; Iman et al., 2017). Besides that, those cells release growing factors, cytokines and extracellular vesicles that, by exercising their paracrine regulatory functions and autocrine regulation, have regenerative effects, reduce inflammation and promotes tendon healing (Torres-Torrillas et al., 2019; Rhatomy et al., 2020; Lu et al., 2021).

This study presents itself with the purpose to revise the existing literature towards the use of mesenchymal stem cells as a treatment to lateral epicondylitis, summarizing the existing clinical evidences and evaluating its efficacy, as to create a clear vision of the current researches and its progress in such therapy.

2. Methodology

It was conducted, in July 2022, literature research for original publications and high level of scientific evidence papers in the following databases, Medical Literature Analysis and Retrieval System Online (MEDLINE) and Cochrane library. Besides that, manual researches were made using the references cited by the studies selected. The Medical Subject Headings (MeSH) used were: stem cells, tennis elbow, tendinopathy, treatment outcome and tendon.

The narrative review makes it possible to synthesize knowledge on a given subject, promoting the deepening of knowledge and leading to critical thinking, relevant points to daily practice in health (Barros & Lehfeld, 2000).

There were no financial incentive, conflict of interests or need of the ethics committee approval to conduct this study. The detailed research strategy is detailed in Table 1.

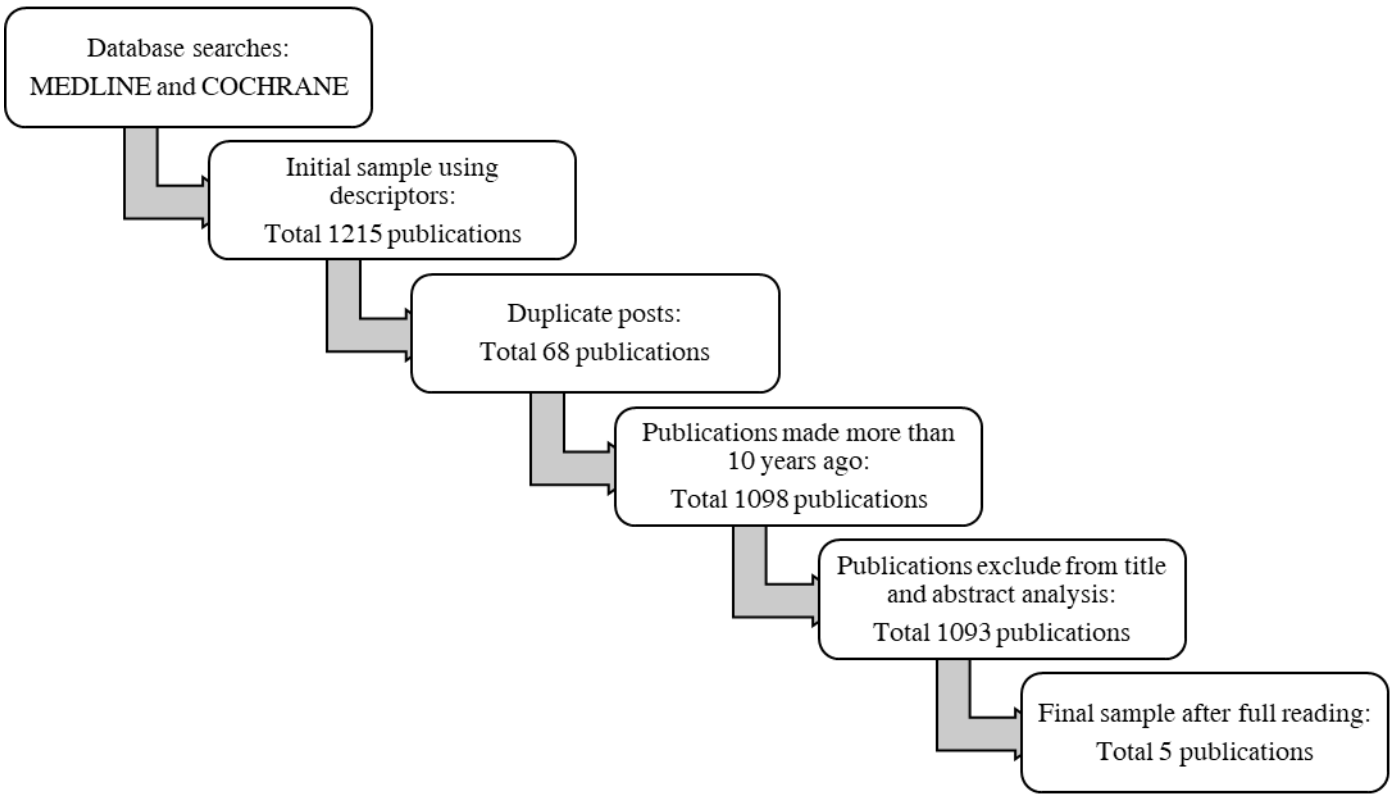
Table 1 - Research strategy and results according to the database.

Database	Mesh Terms	Filter	Results
MEDLINE	#1: (Tennis elbow or tendinopathy) and stem cells #2: (Tennis elbow or tendinopathy) and treatment outcome #3: Tendon and stem cells #4: Tennis elbow	Since 2012 Free full text Comparative study Controlled clinical trial Meta-analysis Observational study Randomized clinical trial Systematic review	357
Cochrane library	#1: (tennis elbow or tendinopathy) and stem cells #2: (Tennis elbow or tendinopathy) and treatment outcome	Since 2012 Trials	741

Source: Authors (2022).

The inclusion criteria used for sample selection were: articles published in the period from 2011 to 2021, with themes focused on use of mesenchymal stem cells to treat lateral epicondylitis or other human tendon diseases. Studies that addressed other existing treatments were also selected. The following were excluded during the search: duplicate productions, editorials and letters to the editor. The inclusion criteria adopted were applied after reading the selected texts in full, Figure 1, below, presents a flowchart that demonstrates the step by step taken to reach the number of articles established for the review.

Figure 1 - Trajectory articles found, 2022.



Source: Authors (2022).

3. Results

Because there is a small amount of studies about mesenchymal stem cells use to treat lateral epicondylitis, articles about MSCs use in other tendon diseases were also included.

Just to give a parameter of the "Research Corpus", Table 2 entitled - "List of studies selected for analysis according to the order: author, country, type of study and surgical procedure" is presented below in a synthetic way and discussed in the analytical aspect in the theoretical foundation of this article.

Table 2 - List of studies selected for analysis according to order: author, type of study, tendon disorders, sample size, MSCs origin and follow up.

Authors	Study design	Tendon disorders	Sample size	MSCs origin	Follow up
Lee et al[3]	Prospective study	Lateral epicondylitis	12	Adipose tissue	12 months
Singh et al. [21]	Prospective study	Lateral epicondylitis	26	Bone Marrow	12 weeks
Havlas et al. [22]	Prospective study	Rotator cuff tear	8	Bone marrow	6 months
Jo et al.[23]	Prospective study	Partial rotator cuff tear	18	Adipose tissue	6 months
Pascual-Garrido et al.[24]	Prospective study	Patella tendinopathy	8	Bone marrow	5 years

Source: Authors (2022).

Lee's et al (2015) prospective study was the first to reveal allogenic MSCs collected from adipose tissue therapeutic potential in LE treatment. Half of the patients received a million of AMSCs (group 1) and the other half received 10 million AMSCs (group 2), the groups were monitored in the days 0 and 3 and in the 2nd, 6th, 12th, 26th and 52nd weeks after the

injection. The treatment efficacy was evaluated through Visual Analogic Scale for pain (VAS), Mayo modified performance index for elbow and ultrasound (US) images. Elbow pain reduced significantly and gradually. The performance enhanced considerably until the 6th week, stabilizing after that. At last, but not least, the US had shown an expressive reduction of the lesions until the 26th week, but in the 52nd week, there were observed a small growth of the lesion, compared to the latest exams. No adverse events or any difference between group 1 and 2 were observed.

In the study by Singh et al (2014) the efficacy was measured for the Patient-rated Tennis Elbow Evaluation (PRTEE), that consists in a scale of a hundred points, being "0" equivalent of no pain at all and "100" equivalent of the worst pain the patient ever felt. The patients were monitored in the 2nd, 6th and 12th weeks after the injection. Before the treatment, the average punctuation in PRTEE of all patients were almost 70 points. In the 2nd week, a decrease of 30 points were observed, in the 6th week another decrease of 20 points were observed and in the 12th weeks another 10 points reduce were seen, which represents a significant pain improvement.

The prospective study conducted by Havlas et al (2015) attested the efficacy of autologous MSCs, obtained from bone marrow and applied during an arthroscopic procedure to repair rotator cuff tear. The patients were observed in this study and followed in the 6th week, 3rd and 6th month after the procedure, through physical exam, visual analogic scale (VAS) for pain, questionaries and MRI. The results improved significantly after the 6th weeks and the 6th month of the surgical approach, the VAS score indicated the absence of pain and the MRI showed a totally healed tissue. Furthermore, no adverse effect was observed during the study.

The study by Jo et al (2018) was divided in two halves, in which the first half of patients (9) were subdivided in 3 groups of low (10 million MSCs), medium (50 million MSCs) and high (100 million MSCs) doses of MSCs injections. These groups were followed for 28 days after the injection. Then, in the second phase of the trial, the second half of the patients underwent the treatment, and received only high doses of MSCs injections. After 6 months, all of the patients were evaluated using pain and function scores, MRI and arthroscopy. A significant reduction of pain and of the size of the lesion were observed in the groups that underwent medium and high doses of MSCs injections. The group that received low dose injections also showed improvement in all of the exams, but not as expressive as the other groups.

At last, in the prospective study conducted by Pascual-Garrido et al (2012), the patients' follow-up lasted 5 years, in the first two years pain and lesion size improvement were observed, after that, no difference was noticed.

4. Discussion

All of the five studies analyzed had shown positive results, demonstrating the potential of MSCs as a treatment for LE and other tendon injuries. Although there are few studies towards this theme, and those analyzed in the present review conducted the trials with a small populational sample, the totality of the results had shown a great pain improvement. Furthermore, none of the studies reported significant adverse events, but it doesn't put away the fear of carcinogenic potential of this therapy in the long run, even though there are no concrete studies reporting its appearance (Lee et al., 2015)

There is not yet a consensus towards the number of MSCs that should be administered. While Lee's et al (2015) study have not shown significant difference between lower and higher doses of MSCs, Jo's et al (2018) have shown this difference, mainly between groups with lower dose and groups with medium and high doses. When analyzing the action time needed to see results and the effect of MSCs, there were no discrepancy in most of the studies. The study conducted by Lee et al (2015) have shown substantial improvement of pain until the 6th month of follow up, nonetheless, the study of Pascual-Garrido et al (2012), had shown that the pain improved expressively until the 2nd year, stabilizing after that.

When analyzing the type of transplant the patients underwent, in four (Sigh, et al., 2014; Haylas et al., 2015; Jo et al.,

2018; Pascual-Garrido, et al., 2012) of the studies were autologous transplant and one was an allogenic transplant. Lee et al (2015) defends the use of autologous MSCs based on the practicality it offers, since the cells are available to use without invasive preparation. Besides that, an ischemic cardiopathy treatment study compared the types of MSCs, both autologous and allogenic mesenchymal stem cells, showed the same efficacy and safety between both (Hare) (Hare et al., 2021).

Both Lee et al (2015) and Havlas et al (2015) studies observed clinical improvements happening (6th week) before the lesion healing (6th month). This result demonstrates MSCs anti-inflammatory effects, that can occur even before the tissue is completely healed (Lee et al., 2015; Torres-Torrillas et al., 2019). However, the exact mechanism these cells function to heal the tendon was not yet fully elucidated (Pascual-Garrido, et al., 2012).

5. Conclusion

Mesenchymal stem cells therapy has shown its efficacy to improve pain, function and to reduce the lesion itself in patients with lateral epicondylitis and other tendinopathies, making it possible to consider this therapy as an alternative treatment for patients that don't answer to conventional methods. However, given the lack of existing clinical trials that attest this therapy efficacy, some doubts still remain, such as what type of transplant is better? Where should the cells be extracted from, bone marrow or adipose tissue? How many MSCs should be used in each injection? How safe is it? What are the long-term effects of this therapy? Only by answering these questions, we can assure the therapy's real safety and widely use.

It is also worth mentioning that given the vastness of the theme and the depth of the subject, this alone is not exhausted, thus, other studies and/or researchers may bring future contributions, with deepening in other methods of bibliographical research; such as: systematic, integrative, bibliometric, among others.

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