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Review Article

A Review on the Evidence of Stem Cell Therapies in Tendon Disorders

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1. Abstract

1.1.Purpose: The aim of this review is to explore what has been researched and published to date on stem cell therapies as a valid treatment for tendon disorders.

1.2.Materials and Methods: We searched through databases MEDLINE-PubMed, Cochrane Library and trial registers in ClinicalTrials. Gov, using the key search terms stemcells, sports, tendinopathies and treatments.From 71 studies found only 4 were included in this systematic review.

1.3. Results: The stem cell therapy group scored significantly better VAS, AOFAS and VISA-A versus other injective therapy ($p<0.05$). The second trial usedallogenic adipose-derived mesenchymal stem cells on human elbow epicondyle tendons. This trial used two groupsof mesenchymal stem cells with different concentrations.Elbow pain was significantly decreased throughout the observation period ($p<0.01$).VAS scores from day 0 to week 52 were significantly lower in both groups. MEPI (Mayo Elbow Performance Index)raised significantly to week 26 and maintained stable to week 52 follow up in both groups. The third trial has published results on a stem cell therapy on human Achilles tendons but as we were unable to access the full report, it isexcludedfrom the results section. This review analyzed four case studies using different methods and different stem cell types, mesenchymal and bone marrow cells.

1.4. Conclusions: Current evidence of stem cell therapies in the treatment of tendon disorders and injuries is still in its early stages.

2. Introduction

Tendinopathies or tendon disorders are a clinical syndrome describing overuse tendon injuries characterized by a combination of pain, swelling, and impaired performance. This condition has been extensively researched, and whilst anatomical and clinical aspects are well established, the physiopathology of its regeneration process after acute injury or chronic degeneration, is still to be fully understood, hindering the ability to find effective treatments in a very common but hard to treat condition.

In broad terms, what is being used nowadays in clinical practice to treat tendon disorders range from; resting and icing, NSAIDs, physiotherapy and specific stretching exercises, shockwave therapy, biological therapies mainly autologous Platelet Rich Plasma Factors (PRPs), corticoid-therapy and surgery.However none have a proven link between injury and their application in a systematicmanner, so treatments have evolved into a broad spectrum of approaches. Currently there is no consensus on a clinical guideline for practitioners and sports professionals on how to treat specific tendon disorders, and how to evaluate the recovery with a systematic approach.

Biological therapies are an emerging field in biomedicine and tissue regeneration; both PRPs and stem cells therapies are currently being researched to assess their potential to grow or repair new

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tissue. In the case of PRPs they are already being used in clinical practice and there is a growing number of studies to support this. Regarding stem cells, research is at an early stage in human trials, however there is a considerable amount of animal studies with encouraging results.

So the aim of this review is to explorewhat has been researched and published to date on stem cell therapies as a valid treatment for tendon disorders, and reasons why there are still only limited number of studies published on human trials and the challenges being encountered.

3. Materials and Methods

Evidence of the effect of stem cell therapies in tendon derived injuries has been systematically reviewed in this paper from February 2015 until February 2019.

We searched in MEDLINE-PubMed using the search words "stem cells" AND "sports" AND "tendinopathies", 57 studieswere identified.We also searchedCochrane Library using the words "stem cell" AND "treatment" AND "tendinopathy" AND "sportive",10 trials and 1 reviewwere identified. We furthermore searched ClinicalTrials.gov where a total number of 3 unpublished trials were found, although none of them had reported results.

A total of 71 studies were identified, 61 were filtered after eliminating duplicates for screening purposes, to which we applied our inclusion criteria (Table 1). These had to be published human studies.Only high quality studies such as randomizedcontrolled trials, meta-analysis and systematic reviews were included. Patients required to have an established and diagnosed tendinopathy. And the intervention had to include an injected stem cell therapy.

Finally a total number of 57 reviews were eliminated. 9 were based on animal or veterinary clinical trials,or in vitro trials. 15 were eliminated because they did not include stem cell injected therapy as their main intervention procedure and/or didn't relate to a tendinopathy. The 3 trials identified in ClinicalTrials.gov hadn't reported any results. And a total of 30 studies were excluded dueto poor validity, such wereexpert reviews, opinion articles and case studies, all with a poor methodological approach for the purpose of this review. However we excluded 1 study from this screening [12], It's an Open Label Trial, with 12 participants,it is aligned with our inclusion criteria and responds to our question. Notwithstanding its limitations, we must highlight the difficulties in conducting randomized clinical trials of the nature of this intervention; injective therapies of cultured allogenic mesenchymal stem cells. We ended up with a total of 4 eligible studies for full text evaluation(Figure 1); Flowchart search methodology for summary purpose.

Table 1: Inclusion criteria

Table 1.Inclusion criteria.

- Published human studies.
- Randomized controlled trials, clinical trials, meta-analysis and systematic reviews.
- Patients with established and diagnosed tendinopathy.
- Injection therapy using stem cells as their main intervention procedure versus other injective therapies.

4. Results

We believe the analysis proposed in this paper has been strictly following inclusion criteria in line with previous systematic reviews in order to have some consistency when comparing the published results.

We specifically have not explored the biological treatment regarding platelet rich plasma(PRP), as it is not the scope of this review, and there is more evidence regarding this therapy in today's scientific literature as quoted previously. Although we will find similarities as both are injective therapies that treat tendinopathies and both are biologically based.

(**Table 2**) underlines the main characteristics of the studies selected, main outcomes and adverse effects. Twotrials used adipose derived mesenchymal stem cells, with the exception of the systematic review that analyzed four case studies using different methods and different stem cell types; mesenchymal and bone marrow cells. The third trial DeGirolamo 2016 will not be included in the study characteristics and results section as we were not able to access the details of the full study, or the full report has not been published. We can't certify that the findings were reproduced in a proper setting.

The study conducted by Uselli et al.[13], aimed to compare the effect of a single stem cell injection with another injective treatment, a Plasma Rich Platelets (PRP) treatment. They recruited 44 patients, 23 were assigned to the PRP group and 21 to the stem cell group. The groups were similar between each other ($p<0.05$) and there were no losses during the study. Both treatments showed improvement with respect to baseline. From the two groups, the stem cell therapy group scored significantly better VAS(Visual Analogue scale), AOFAS (American Orthopedic Foot and Ankle Society Score) and VISA-A (An index of the severity of Achilles tendinopathy) at 15 and 30 days in comparison to the PRP group ($p<0.05$). Further time points showed that scores were not significantly different between the two groups. However, despite clear positive outcomes of both therapies compared to baseline, neither group showed improvements in the radiological findings.

Table 2. Study Outcomes

Stem Cell Therapy	Study Object	Outcomes	Significance	Adverse Effects	Study Type	Reference
Adipose derived stem cells SVF (stromal vascular fraction)	Human Achilles tendon.	The injection of stem cells (SVF) provided a significant clinical improvement in terms of pain relief and function restoration. VAS pain scale	P<0.05*	No serious side effects or adverse events were observed.	Randomized controlled clinical trial at a 6-month follow-up.	Usuelli et al. 2016
Autologous Adipose derived stem cell SVF	Human Achilles tendon.	Adipose-derived stem cells (SVF) are safe and effective treatments for Achilles tendinopathy.		No side effects were observed in neither groups.	Randomized Prospective Clinical Trial	DeGirolamo et al. 2016**
Allogenic adipose-derived Mesenchymal stem cells	HumanElbow epicondyle tendon	Elbow pain during activity was significantly decreased throughout the observation period .	P < 0.01	No significant adverse effects were observed.	Pilot Trial. Open label Study.	Sang Yoon Lee, et al. 2015.
Bone Marrow and Allogenic Adipose derived stem Cells	Human Achilles tendon, rotator cuff and elbow epicondyle	There is no evidence to support the use of stem cell therapy in tendon disorders.			Systematic Review	Pas et al. 2017

The trial conducted by Sang Yoon Lee et al[12],is an open label study to determine the safety and efficacy of two different doses of mesenchymal stem cells for the treatment of lateral epicondylosis. To test the safety, a conventional 3 + 3 cohort expansion design was used with 2 different doses of cells 10^6 and 10^7. 12 subjects were enrolled into the study and injected with two different doses of stem cells and completed the 52-week post-treatment observation period. There were no significant differences in age, disease duration, VAS scores, MEPI(Mayo Elbow Performance Index), or defect areas between the two groups. Elbow pain was significantly decreased throughout the observation period ($p<0.01$). Even though one of the groups, with higher cell concentration, tended to show more rapid pain improvement from day 0 through 26 weeks, no significant differences were observed in VAS scores between the two groups at any of the follow-up visits.VAS scores from day 0 to week 52 were significantly lower in both groups. MEPIperformance index raised significantly to week 26 and maintained stable to week 52 follow up in both groups. And ultrasound axis measurements were reduced from week 0 to week 52 in both groups. Anew ultrasound quantitative methodology was used, as the team were aware of the difficulties to detect changes with MRI scans in tendon repair models in other studies, like the one quoted previously from Owens et al.[17].Two blinded ultrasonographic examiners measured the areaswitch the largest lesions. Changes in defect areas in the transverse and longitudinal axis were reduced considerably between week 0 and week 52 follow up ($p<0.05$).

Finally, the review conducted by PasH et al[14], systematically reviewed the evidence for stem cell therapies in tendon disorders retrospectively from 2016. Four published and three unpublishedorpending trials were found. No unpublished data was available. Two trials evaluated bone marrow-derived stem cells in rotator cuff repair surgery and found lower retear rates compared with historical controls or the literature. One trial used allogenic adiposederived stem cells to treat lateral epicondylar tendinopathy. Improved MEPI (Mayo Elbow Performance Index), Visual Analogue Pain scale and ultrasound findings after 1-year follow-up compared with baseline were found. Bone marrow-derived stem celltreated patellar tendinopathy showed improved International Knee Documentation Committee, Knee injury and Osteoarthritis Outcome Score subscales and Tegner scores after 5-year follow-up. One trial reported adverse events and found these to be mild (swelling and effusion). All trials were at high risk of bias and only level 4 evidence was available. The conclusions of the systematic review was that there was no robust evidence for the use of stem cells for tendon disorders. So clinical practice is currently not advised.Based on level 4 case studies reviewed from 2012 to 2015.

5. Discussion

As we highlighted at the beginning, tendinopathies are a complex and difficult condition to treat. Our initial hypothesis based on extensive literature states that the lack of a systematic approach on the management of tendon disorders, is mainly due to the lack of effective treatments. This has given room to new biomedical approaches such as growth factors and stem cell therapies. We believe there is a need to understand what these biological treatments mean, how stem cells are being used, their risks and effectiveness. The inflammatory and immunological environments and how they can be applied to the human body for healing purposes. Hence the aim of this review is to understand further what are the current findings of stem cells and their use in human tissue regeneration.

After evaluating the three studies subject of this review, we have been able to grasp the current picture of these biological therapies in treating tendinopathies today, and also identifiedsome of the main challenges encounteredas to why we might not be seeing more trials on this nouvelle line of work.

The first obstacle we encounter is the preparation of stem cells. As described by Laprade et al.[15], and published inthe The American Journal of Sports Medicine, some of the barriers encountered are the limited availability of stem cells both for allogenic or autologous treatments, as there is a needto expand the colonies in vitro before theinjection. Moreover,another challenge would be the nature of the production of stem cells, its

complexities and the cost inherent to the process.Others go further stating the great difficultiesof producing stem cell cultures as these are highly plastic. Changing their state is an inherent part of their biology, and therefore the biggest challenge is to reproduce in vitro the body's stem cell environment. One of the reasons for including an open study in this review Lee et al[12], was due to the fact that it had applied a clinical trial 3+3 methodology for testing the safety of stem cell therapies, shedding some light on preparing a trial with stem cellsby using two different groups with two different quantities of cells, giving us a first indication, albeit on 12 patients only, ofthe methodology used andits application on humans.All tests were approved by the Korean Food and Drug Administration.

A second group of challenges that may be hindering the ability of research teams to invest more in human trials, are some of the ones stated by Uselli et al.[12]. This team have been one of the few, if not the only one, reproducing a human randomized trial on stem cell therapy treatment of a tendinopathy.With positive outcomes demonstrated both for the intervention group with mesenchymal stem cell therapy and the comparison group with plasma rich platelets, both showing positive results in all the pain and performance scales measured. And consistent to other reviews such asOwens et al. 2012, with no improvements in the radiological findings. This clinical-radiological dissociation could be explained by the fact that stem cells and PRP therapies are strong factors in modulating inflammatory and immunological responses, but not necessarily modulated tissue regeneration. However we also have other studies that have shown radiological improvements as mentioned here in this review by Lee et al, albeit a limited numbers of patientsand other studies also showing positive results.

However the issue still resides and it is twofold; first the complexity of the diagnosis of a tendinopathy due to the inconsistencies between the clinical symptoms and the imaging results, like seen in other disciplines like osteoarthritis. And secondly, that there is no consensus on a gold standard for the diagnosis of a tendinopathy. As normally pain, location of pain and pain during certain moves is currently used as a reference when diagnosing the lesion. Overall there is disparity in the literature regarding radiological findings when detecting tendon tears or post treatment improvements. More work should be done tocome up with a consensus on a gold standard clinical and/or radiological technique in order to have a consistent measuring tools for the everyday clinical practice and the future of clinical trials in this field.

The third group of challenges comes down to the feasibility of testing injective therapies in humans. When we think about injecting treatments in oncological patients, the invasiveness of the procedure and its risks, are in some way not the highest priority forpatients or doctors as we are trying to improve a life-threating disease. This is in total contrast with tendon disorders, mostly non-threatening and mostly not completely debilitating. Which makes the risks of invasive treatments a higher order of importance when balancing the risks and benefit ratio.This could be an obstacle when recruiting patients in larger studies. Truth being told, there are many injective therapies which have not shown adverse effects, or the ones encountered have been marginal. In both trialsand the systematic review analyzed, alldeclared finding no significant adverse effects.

To answer the question proposed in this review; current evidence of stem cell therapies in the treatment of tendon disorders and injuries is still in its early stages.Therefore we can't conclude that stem cell therapies are currently an approach to be used in clinical practice because there isan insufficient number of studies to support any opinion in favour or against the use of stem cells. We therefore follow recommendation sin line with Pas et al [14]and other groups of experts, Laprade et al.[15], the American think tank group on Biologic Treatments for Sports Injuries.In being cautious with current stem cells therapies as there is a need to understand further cellular interactions both of autologous and allogenic stem cells and side effects.As well as a systematic way to compare and measure objectively their effectiveness on tissue regeneration and pain modulation in the management of tendon disorders.

Table 3: Recommendations cited by the authors

• Future human trials should include a large number of patients. • Allocation concealment and control groups necessary as methodological validity is key for implementation in clinical setting • Type of stem cells, extraction and expansion methods should be agreed. • Further analysis on imaging and diagnosing techniquesof tendinopathies. • Consensus on a gold standard for screening and evaluating purposes.

We also conclude that even with all the limitations encountered and described above in this discussion, there are also very promising outcomes that should encourage researchers to work to overcome these obstacles. We have included a list of recommendations (Table 3) made by the authors included in this review. First, that human trials should include a higher number of patients for more robust results. Allocation concealment should be introduced and controlled groups established. Methodological validity is key to be able to use the findings and implement them in a clinical setting. Consensus on a specific type of stem cell, its extraction methods and expansion techniques should be agreed to be used in trials across the board. And specific work should be done on imagining and diagnosing techniques, which would also require agreeing on a gold standard for screening and evaluating purposes.

Regenerative medicine is the future, and stem cell therapies should continue to be a key line of research in the future ofSports medicine, Traumatology and other related disciplines.

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