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Mesenchymal stem cells transplantation in the treatment of tendon disorders

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Abstract
Introduction and purpose: Tendon disorders are conditions that lead to pain, reduced mobility, and are often associated with recurrences and complications. A novel therapeutic approach for these conditions is the transplantation of mesenchymal stem cells (MSCs) into the affected area. This paper presents knowledge on the use of MSCs for the treatment of tendon disorders. Additionally, it presents advances in research regarding the application of MSC transplantation in the following conditions: rotator cuff tendon injuries, lateral epicondylitis, Achilles tendon disorders, and patellar tendon injuries.
Material and methods: A review of the PubMed and Google Scholar databases was conducted.
Results: It is suggested that MSCs support tendon regeneration through the regulation of inflammatory processes, their capacity to differentiate into various cell types, their influence on collagen synthesis, and their effect on the migration and proliferation of tenocytes. Research indicates that transplantation into damaged tendons enhances tendon function and reduces pain. While many studies have not reported the occurrence of side effects, some have noted such cases.
Conclusions: Further research is required to develop a deeper understanding of the role that MSCs play in the treatment of tendon disorders. Additionally, there is a need to establish precise treatment protocols and evaluate the safety of this procedure.

Keywords: Mesenchymal stem cells, tendon injuries, tendon rupture, stem cells

1. Introduction

Tendon disorders lead to pain and reduced mobility that affect daily functioning and impair the quality of life. Ineffective treatment, often associated with relapses and complications, significantly burdens the healthcare system. These issues have led to the exploration of new treatment methods as a support for the primary treatment. A novel therapeutic approach for this group of disorders uses the properties of Mesenchymal Stem Cells (MSCs) derived from bone marrow or adipose tissue. Studies on the application of MSCs in regenerative medicine are ongoing, especially in the treatment of disorders such as hard-to-heal wounds, musculoskeletal repair, peripheral nervous system injuries, liver diseases, corneal diseases, tracheal diseases. [1] The safety, efficacy, and side effects of this treatment are still being studied. This paper presents a summary of information on the use of mesenchymal stem cells in the treatment of tendon disorders.

2. Material and methods

A review of the PubMed and Google Scholar databases was conducted. We reviewed most of the articles exploring findings and studies about the treatment of tendon disorders using mesenchymal stem cells. Additionally, the literature on tendon diseases, as well as the physiology of mesenchymal stem cells and their impact on these disorders, has been reviewed.

3. Results

3.1 Tendon disorders - risk factors and epidemiology

In musculoskeletal medicine, tendon disorders are often encountered. It is suggested that excessive load and overuse of the tendon can result in damage to the cells and ECM (Extracellular Matrix) and disruption of the collagen structure, all of which contribute to tendon injury. [2] Other risk factors are drugs, especially steroids [3], systemic diseases - such as diabetes mellitus or amyloidosis, genetic predispositions, male sex, training errors, previous injuries, body weight, muscle strength, etc. [4] The tendons that are most commonly impacted include the rotator cuff in the shoulder (51,000 incidents), the Achilles tendon (44,000 incidents), and the patellar tendon (42,000 incidents). [5] Due to the fact that sport and physical activity have an increasing role in modern societies, the risk of tendon injuries has increased. [6]

3.2 Tendon disorders - management

The treatment of tendon disorders may be conservative or surgical. The method of treatment is, of course, determined by the type, etiology, and severity of the condition. Pharmacological treatment includes NSAIDs or steroid injections, both with their specific possible adverse effects. An important role is also played by physical therapy - cryotherapy, ultrasound therapy, and laser therapy. [7] While the above-mentioned treatment methods have shown positive outcomes in tendon injury management, they are unable to fully restore the structure and function of the damaged tendon. Moreover, the tendon tissue after repair usually does not reach the same condition as before the disease. [8]

3.3. Mesenchymal stem cells (MSCs) - definition and role

Mesenchymal stem cells (MSCs) are a type of stromal cells known for their capacity to self-renew and differentiation into multiple cell types. [9] There are numerous sources of these cells. The most common in current protocols are bone marrow which provides BMSC (Bone Marrow Stem Cells) and adipose tissue rich in ADSCs (Adipose-derived Stem Cells) due to the ease of material collection and the large number of cells obtained. [10] The source of BMSCs is the bone marrow from the iliac crest, which requires the use of a specialized trocar. ADSCs are derived from adipose tissue, usually from the abdominal region. The harvested material must then undergo specific procedures, including centrifugation and purification, to isolate the ADSCs. Other origins of stem cells are peripheral blood, placenta, umbilical cord, etc. [11] Other new sources and harvesting methods of MSCs are still being studied. A separate group of stem cells is ESCs (Embryonic Stem Cells) derived from embryos, capable of differentiating into most cell varieties, which play a significant role in the field of tissue repair and restoration. [12] However Blum et al. highlight the potential risk of teratoma development after ESCs transplantation and necessity of differentiating ESCs into mesenchymal lineages before this procedure and elimination of any remaining undifferentiated cells from ESCs extract prior to their use. [13] There are also ethical issues related to the extraction of ESCs for such procedures due to the destruction of embryos during their collection. Another group of stem cells used in regenerative medicine is iPSCs (Induced Pluripotent Stem Cells). This is a type of pluripotent stem cells that have been artificially generated from non-pluripotent cells through the forced activation of specific genes within these cells. [14]

The use of these cells in regenerative medicine is associated with fewer ethical issues due to the fact that they are derived from cells that have already undergone differentiation. Nevertheless, similar to ESCs, their application still poses a potential risk of teratoma development. [15]

Stem cells are believed to play a role in the healing of tendons by supporting regeneration. [16]. They are hypothesized to regulate inflammation processes by modulating the immune response. This occurs through the regulation of macrophages by MSCs via direct cell-to-cell contact or paracrine secretion of soluble factors (TGFbeta2, IDO, PGE2). Furthermore, they suppress T lymphocytes, mast cells, and NK cells. [17] This leads to the polarization of M1 macrophages into M2 macrophages, which may result in an anti-inflammatory effect. [18] Modulation of the inflammatory environment by MSCs allows ordered deposition of ECM (Extracellular Matrix). [19] Despite numerous studies on how MSCs regulate macrophages, the precise molecular pathways are not completely understood, and the exact mechanisms of tendon regeneration are still to be clarified. In addition to their immunoregulatory functions, the regenerative role of MSCs is also based on their ability to differentiate into various cell types under appropriate conditions. [20] These cells have the potential to transform into tendon-like cells and support the restoration of tendon function by secreting their own proteins. [21] Furthermore MSCs may have an influence on the synthesis of collagen. It is demonstrated that the injection of MSCs after injury of tendon leads to the secretion of factors such as TGF-β or bFGF, which promote the remodeling of the extracellular matrix and collagen synthesis at the affected site. [22] Moreover, MSCs may influence the proliferation and migration of tenocytes - cells that synthesize ECM components at the site of tendon injury - fibronectin and proteoglycans. [22]

3.4. MSCs in the treatment of tendon disorders

Researchers have demonstrated that MSCs offer a potential therapeutic approach for treating tendon disorders. [23] Firstly, MSCs are collected from their sources, such as bone marrow or adipose tissue. Subsequently, they are administered to the patient after the use of various techniques of preparation or purifying MSCs. Moreover, there are studies in which MSCs are injected along with other compounds, such as growth factors, which are thought to promote the expression of paracrine factors. [24] Most of the current research on MSCs and their connection to tendons primarily focuses on animal models. Fewer studies address the use of stem cells in the treatment of tendon disorders in humans.

3.4.1 Rotator cuff tendon disorders

Several studies have been conducted on human subjects evaluating the effects of MSC therapy for treating rotator cuff tendon disorders. It appears that this group of tendons is the subject of the largest number of studies describing the discussed therapy in humans, compared to other body regions. One such study is that by Lamas et al., in which a xenogenic scaffold enriched with BMSCs was used to treat full-thickness supraspinatus tendon tears. [25] In this study, a significant improvement in the Constant score, a measure of therapeutic efficacy, was observed compared to preoperative data. However, the study was discontinued due to the occurrence of adverse events.

There have also been attempts to inject ADSCs into these areas in cases of partial rotator cuff tears, where improvements in function and reduction in shoulder pain were observed without any adverse effects. [26,27] Additionally, a study evaluating the effectiveness of rotator cuff repair enhancement using BMSCs injected during arthroscopy observed an increased healing rate and improved quality of the repaired tissue compared to the control group, as well as a lower incidence of tendon ruptures in the following years. [28] However, another randomized controlled trial assessing the impact of MSCs on partial supraspinatus tendon tears in terms of pain, shoulder function, and tear size did not show statistically significant differences compared to the control group - there was no evidence that stem cell injection was more effective than the control injection. [29] Another study evaluating the efficacy of treating partial rotator cuff tears with unmodified ADSC injections demonstrated statistically significant superior treatment outcomes compared to steroid therapy. [30] In certain instances, BMSCs were combined with PRP (Platelet-Rich Plasma) and injected into the region of the rotator cuff, resulting in observed improvements in both function and pain. [31] Due to the limited number of studies available, it remains challenging to definitively assess the effectiveness of ADSCs and BMSCs therapies in the treatment of rotator cuff disorders.

3.4.2 Lateral epicondylitis (tennis elbow)

Lateral epicondylitis, also known as tennis elbow, is a disorder characterized by pain and sensitivity of the common extensor origin of the elbow. Conservative methods are often ineffective in managing this condition. The use of stem cells for the treatment of this condition in humans has been documented in several studies. In 2015, Lee et al. evaluated the safety and efficacy of treating this condition with ADSCs combined with fibrin glue and injected into the site of the lesions. No severe adverse effects were reported, and improvements were observed in pain, function, and structural defects. [32] Singh et al. observed a significant reduction in the PRTEE (Patient-related Tennis Elbow Evaluation) score following a single injection of bone marrow aspirate, indicating considerable improvement. [33] Notably, in the first study, a faster improvement in pain and an earlier plateau in results were observed in the group receiving a higher dose of ADSCs (10^7 cells) compared to the group with a lower dose (10^6 cells).[32] However, both studies lack a control group, which limits the strength of the evidence. Kohury et al. conducted a study on 18 tennis players suffering from chronic, treatment-resistant, non-surgical tennis elbow. The participants were injected with isolated ADSCs at the site of tendinopathy, in addition to undergoing physiotherapy. After a 6-month follow-up, significant clinical and structural improvements were observed following the application of ADSCs.[34] As in previous studies, this research also lacks a control group, and the topic still requires further investigation to determine the role of stem cell therapy in this condition.

3.4.3 Achilles tendon disorders

Problems with the Achilles tendon, the biggest human tendon, are frequent and affect both physically active individuals and those with a more sedentary lifestyle. Studies on the role of cell-based therapy in treating Achilles tendon disorders have been conducted on human models. In one such study, 10 patients with pain in the middle part of the tendon and swelling lasting for over 6 months were treated with BMSCs at the affected site.

During the study, no adverse effects were observed, and improvements were noted in the measured indicators of EQ-5D-5L (EuroQol 5-dimensions 5-levels), EQ-VAS (EuroQol Visual Analogue Scale), and MOXFQ (Manchester Oxford Foot and Ankle Questionnaire). [35] In a previously conducted study, 15 patients with resistant Achilles tendon tendinopathy were treated with BMA (Bone Marrow Aspirate) concentrate, showing an improvement in the measured NRS (Numeric Rating Scale) score. [36] A similar BMA concentrate was used in the treatment of acute Achilles tendon injuries in a group of 27 patients, showing positive treatment outcomes, no recurrent ruptures, and the possibility of early mobilization. [37] Acute Achilles tendon rupture was also treated in a group of patients using SVF (Stromal Vascular Fraction) rich in ADSCs, where significantly better results were achieved compared to patients treated with PRP after 15 and 30 days. [38] Studies on animal models have shown that ADSCs may support the repair of Achilles tendon injuries by enhancing the expression of genes involved in the synthesis of collagen types I and III, even in the absence of observable changes in histological analysis. [39]

3.4.4 Patellar tendon disorders

There have been studies exploring the potential of stem cell therapy for treating patellar tendon disorders. In 2005-2006, eight patients with chronic patellar tendinopathy resistant to conservative treatment underwent a procedure where bone marrow stem cells (BMSCs) were harvested from the iliac crest and injected into the site of injury. The majority of clinical outcomes showed statistically significant improvement, and seven out of the eight patients indicated that they would opt for the procedure again. [40] A prospective, double-blind, randomized clinical trial involving 20 patients with chronic patellar tendinopathy resistant to conservative treatment demonstrated significant improvements in average VAS scores and a notable reduction in pain during sports activities. In the BMSCs group, there was a statistically significantly greater improvement in tendon structure observed on ultrasound, as well as significant evidence of tendon structural restoration on MRI compared to the LP-PRP (Leukocyte-poor platelet-rich plasma) group. [41] The Lp-PRP group was then offered treatment with BMSCs, and after 12 months a highly significant clinical improvement was observed, along with an enhancement in tendon structure as seen on MRI. [42]

3.5. Adverse effects

The issue of adverse effects related to the treatment of tendon disorders with mesenchymal stem cells remains underexplored in the literature. Most studies report no adverse events associated with the described procedures. However, one of the previously mentioned studies investigating the treatment of full-thickness rotator cuff tears with MSCs isolated from bone marrow aspirate indicated that the trials were discontinued due to the occurrence of adverse effects in 3 out of 8 patients in the treatment group and 1 out of 5 patients in the control group. Reported complications included the formation of supraclavicular cysts and the development of subacromial inflammatory tissue. Additionally, tendon re-rupture occurred in 3 out of 5 patients in the control group and 5 out of 8 patients in the treatment group. [25] Another previously cited study on the use of ADSC injections for the treatment of rotator cuff disorders reported an adverse effect in the form of back pain in 3 patients. [26] In the study by Lee et al. [32] on the treatment of lateral epicondylitis using ADSCs, mild swelling at the injection site was observed in six patients, which resolved spontaneously within two weeks.

Additionally, two patients developed elbow joint effusion, which also resolved spontaneously within one month. One participant reported delayed elbow pain seven weeks after the injection, which subsided with rest and pain medication. The above examples demonstrate that although allogenic mesenchymal stem cell transplantation is described as a treatment method with minimal side effects, such side effects do still occur. Therefore, further research on the safety and potential adverse effects of this treatment for tendon disorders is necessary.

4. Conclusions

Research suggests that stem cells may accelerate tendon regeneration and play a crucial role in regenerative medicine. It is proposed that following treatment with ADSCs or BMSCs, patients experience faster recovery of functional ability and improved pain outcomes. This would enable quicker rehabilitation for individuals with tendon disorders and also reduce the risk of re-injury. Some studies also indicate that the regenerative process can be influenced by PRP. However, further investigation is needed into the cellular and molecular mechanisms involved in these processes to better understand the role of MSCs in treating tendon diseases. Additionally, more research is necessary to develop precise treatment protocols and assess the safety of stem cell therapies in humans. This includes optimal cell harvesting techniques, processing methods, transplant cell quantities, transplantation techniques, and other factors that impact the success and safety of treatment. It is also important to evaluate the advantages of this method compared to alternative treatments. Furthermore, potential side effects associated with this therapy, such as the risk of oncological complications in the treated tendon area, should be thoroughly assessed. This would constitute a significant contribution to the field of sports medicine and orthopedic trauma, where tendon diseases are prevalent, often resistant to treatment, and characterized by chronicity.

5. Authors' Contributions Statement:

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Project Administration: A.R., M.P., P.M., M.M., A.C., A.S., K.S., A.K., M.W., N.M.

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