

# Mesenchymal stem cells for the treatment of tendon disorders

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Received 22 May 2013; revised 28 June 2013; accepted 15 July 2013

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## ABSTRACT

**Tendon disorders are associated with increased morbidity and a reduction in the quality of life, especially in people of working age. Recently, a new approach, cell-based therapy, offers promising potential to treat tendon injuries. Mesenchymal stem cells are the most suitable candidates for such therapies due to their capacity to differentiate into cells of mesodermal origin, their paracrine properties and their potential use in autologous transplantation. This review summarizes experimental as well as clinical data focusing on the use of mesenchymal stem cells to treat tendinopathies.**

**Keywords:** Tendinopathy; Tendinosis; Tendonitis; Models of Tendon Injuries; Mesenchymal Stem Cells; Rotator Cuff; Achilles Tendon; Tendon Rupture

## 1. INTRODUCTION

Tendon disorders represent a common diagnostic and therapeutic challenge, resulting in chronic and long lasting problems. The medical nomenclature uses terms such as “tendinosis”, “tendinopathy”, “tenopathy”, “tendonitis”, “tendinosis” and “partial rupture” to describe exactly the same clinical entity, non-ruptured tendon injuries [1]. The term “tendinosis” refers to the degeneration of a tendon without any sign of an inflammatory response, while the term “tendonitis” is associated with an inflammatory reaction in the tendon. It has also been suggested that inflammation may occur early after an injury, but it is then superseded by a degenerative response [2]. Paratenonitis is an inflammation of the outer layers of a tendon, while paratenonitis with tendinosis is the degeneration of a tendon without any inflammatory reaction inside the tendon, but associated with paratenonitis. According

to the duration of the symptoms, we can divide tendon disorders into three subcategories: 1) acute (<2 weeks); 2) subchronic (4 - 6 weeks); and 3) chronic (>6 weeks) [3].

The etiology of tendon disorders remains unclear. A combination of intrinsic and extrinsic factors is the most likely cause, but historically two main theories (mechanical and vascular) have been postulated. In the mechanical theory, tissue degeneration in tendons is associated with the overuse of the tendon tissue within the normal physiological range, which leads to tendon failure. The vascular theory claims that compromising the vascular supply leads to tendon tissue degeneration. Recently, a neural theory has been presented. The overuse of tendons could lead to excessive nerve stimulation and the activation of mast cells via neural endings/mast cell associations, leading to mast cell degranulation and the release of mediators such as substance P [4]. Systemic diseases (rheumatoid arthritis, sarcoidosis etc.), foreign bodies, metabolic and inherited diseases (Ehlers-Danlos syndrome, Marfan syndrome, homocystinuria etc.) or infectious diseases are only rarely the cause of tendinopathy. Ageing, endocrine factors and pharmacological agents can also affect the biomechanical properties of a tendon.

The healing response of a tendon is usually poor. In the acute phase, rapid haemorrhage and inflammation occur, followed by a proliferative phase with fibroblast production of new matrix. Several weeks after injury, the remodelling phase is underway; with the organization and maturation of collagen. Histologically, the signs of tendinopathy include the disorganization and thinning of the collagen fibers, extensive neovascularization and vascular ingrowth. In addition, spindle-shaped fibroblasts change their shape to a rounded, chondrocyte-like shape. Metabolically, the amount of interfibrillar glycosaminoglycans increases, the synthesis of matrix metalloproteinase enzymes is disregulated and the glutamate production in-

creases, which finally leads to altered mechanical properties of the tendon [5].

## 2. ANIMAL MODELS OF TENDON DISORDERS

The development of tendon degeneration is a long-term process, at the beginning clinically silent. To understand the processes that occur during tendon degeneration, even in the early stages of tendinopathy, several animal models have been developed. Models of tendon injuries allow the creation of consistent injuries that can be monitored, evaluated at both the cellular and molecular level, and treated under controlled conditions.

The first group of animal tendinopathy models are “active participation models”. Tendon deterioration is caused by a mechanical stimulus induced by repetitive treadmill running. This treadmill running overuse animal model of tendinopathy is widely used mainly to evaluate changes in the rotator cuff and supraspinatus tendons [6]. Another model for simulating overuse tendon injuries is repetitive reaching and grasping [7]. Both animal models of overuse tendon injuries result in functional changes as well as inflammatory responses.

The second group consists of “passive participation models”. Tendon deterioration is caused without the participation of the animal by using kicking machines to apply passive flexion and extension of the ankle joint of a rabbit under anaesthesia, while simultaneously inducing the contraction of the muscles with an electrical stimulus [8]. This model produces only discrete changes in inflammatory and collagen gene expression and no histopathological changes. Eleven weeks after injury, the changes are proliferative and reparative rather than degenerative in nature. Similar observations have been published by Messner *et al.* [9]. Recent studies used a repetitive long-term muscle stimulation model alone to study molecular changes in the rabbit flexor digitorum profundus tendon [10]. Long-term stimulation of the muscles led to a tendon injury similar to that seen with the treadmill running model. Another passive model of tendinopathy is dropping a weight on the exposed Achilles tendon of a rat under anesthesia [11]. Tendinopathy of the rotator cuff is modeled by compression of the thoracoacromial arch using an Achilles tendon allograft transplanted around the acromion [12] or bone plates transplanted onto the surface of the acromion [13]. These models, when combined with a running wheel, produce consistent significant changes in tendon properties [6,14] and confirm the theory of the multifactorial causation of tendinopathy.

A third group are chemically induced models of tendon disorders. Collagenase application to the tendon is the mostly widely used model. These models produce a consistent and reproducible lesion accompanied by an

inflammatory reaction. The affected tendons are the flexor digitorum superficialis tendon, the deep digital flexor tendon, the Achilles tendon, the patellar tendon and the deep digital flexor tendon [15-20]. The amount of collagenase allows for tight control of the altered parameters. Also, a mixture of cytokines [21], carrageenan, a vegetable polysaccharide [22], corticosteroids [23], perfloracin [24] and prostaglandins [25] have been used to induce a chemical tendon injury.

As the above descriptions make clear, several models of tendon injury have been developed. The main advantage of the active models is their use of repetitive force for developing a tendon injury, which is believed to be the causative mechanism of tendinopathy in humans. The disadvantages of these models are the time consuming process to develop the lesions and a certain inconsistency. Chemically induced models produce more precise lesions and are less time consuming, but the etiology is different than that in humans. More than one model as well as more than one species of animal should be used to evaluate potential treatment of tendinopathy.

## 3. MESENCHYMAL STEM CELLS FOR TENDON TRANSPLANTATION

The discovery of mesenchymal stem cells dates back to the 1960s [26]. Friedenstein and coworkers discovered that bone marrow from the iliac crest, when plated on a plastic dish and after the removal of floating hematopoietic cells, contains a population of fibroblast-like cells, adherent to the plastic, that can differentiate into chondrocytes and osteoblasts. They named these cells mesenchymal stem cells due their ability to differentiate into cells of mesodermal origin [27]. Bone marrow blood consists of two types of stem cells, hematopoietic stem cells and non-hematopoietic mesenchymal stem cells (MSCs). MSCs represent 0.001% of the total bone marrow. MSCs are isolated from bone marrow using their adherence to plastic or their separation by a Percoll gradient [28]. Another source of MSCs is adipose tissue, which produces MSCs similar to bone marrow MSCs, but easier to produce with broader therapeutic capacity [29]. MSCs have also been found in umbilical cord blood [30], dental tissues [31], synovial fluid [32], palatine tonsil [33], the parathyroid gland [34] and the fallopian tubes [35]. MSC transplantation is a promising strategy because of its relative lack of ethical problems and the absence of any development of teratomas, as observed after embryonic stem cell or iPS cell transplantations; in addition, MSCs are easily harvested using a minimally invasive procedure.

MSCs show heterogeneity in culture. They can have a fibroblast-like shape, a giant fat cell shape, a blanket cell shape or a spindle shape and can appear as flattened cells or as very small round cells [36]. The relation between

their morphology and shape remains unclear. According to the International Society for Cellular Therapy, three criteria characterize MSCs: 1) plastic adherence; 2) the expression of CD105, CD73 and CD90 and no expression of CD45, CD34, CD14, CD11b, CD79, CD19 or HLA-DR using flow cytometry; 3) the capacity to differentiate into osteoblasts, adipocytes and chondroblasts [37]. Several studies have been published showing that MSCs have the ability to differentiate into cells of all three germ layers cardiomyocytes, endothelial smooth muscle cells, neural cells, pancreatic beta cells [38-40], but further examination of the properties of these cells is necessary to confirm their full functionality.

MSCs are immune privileged cells expressing a low level of major histocompatibility complex (MHC) class I antigens and no MHC II molecules. For this reason, MSCs do not activate T cell immune responses, but they could be attacked by natural killer cells due to their low MHC I expression [41,42]. This immune phenotype allows MSCs from children to persist in their mothers for decades [43].

The multipotent differentiation capacity of MSCs, their unique immunological properties, availability and easy manipulations have attracted researches to mesenchymal stem cell therapies in many medical fields. MSCs also demonstrate the production of trophic factors [44], minor spontaneous differentiation when expanded *in vitro* [45], and an immunosuppressive effect [46]. These properties predispose MSCs for use in cell replacement, repair and regeneration and immunomodulation in experimental and clinical studies. The list of potential clinical applications is exhaustive, including intervertebral disc repair [47], diabetes mellitus [48], stroke [49], spinal cord injury [50], wound healing and repair [51] etc.

#### 4. EXPERIMENTAL TREATMENT OF TENDON DISORDERS WITH MSCS

The use of mesenchymal stem cells as an effective therapy to repair tendon disorders has been investigated over the last two decades. Pacini *et al.* proved that autologous undifferentiated MSCs implanted into the incompletely damaged tendons of racehorses improves clinical recovery as measured by ultrasonography and the ability to return to racing [52].

Parallel studies have been performed to demonstrate the fate of autologous or allogenic mesenchymal stem cells transplanted into superficial digital flexor tendon injuries in the horse. Post mortem examinations revealed that the MSCs were located mainly within the injected lesions and no visible cell-mediated immune response was observed to allogeneic MSCs in either of the host horses [53].

A series of equine studies comparing expanded cul-

tured MSCs and a mononuclear fraction of bone marrow stromal cells with placebo treatment of experimental tendinitis has been published by Crovace *et al.* [54-56], who reported that treatment with either MSCs or the mononuclear fraction resulted in similar improved healing of the tendon extracellular matrix of in the treated horses.

In another study, Okamoto *et al.* [57] isolated and cultured bone marrow cells (BMCs) from 9 Fisher rats. They compared the use of BMCs, MSCs, or no cells for the treatment of an Achilles tendon defect. The ultimate failure load in the BMC group was significantly greater than in the MSC and control groups at 7 and 14 days. After 28 days, the ultimate failure load in the BMC group was the same as that of the normal tendon. Histologically, these results correlated with more intense collagen III staining after 7 days and a switch to more intense type I collagen staining after 28 days in the BMC group compared with the MSC group. In addition, the expression of TGF- $\beta$  and vascular endothelial growth factor (VEGF) appeared to be greater in the BMC group at 4 days compared with the MSC and control groups.

Kida *et al.* found that bone marrow cells have a positive influence on the healing process of a tendon and tracked the fate and effectiveness of bone marrow cells migrating from drilled bone in the close proximity of the rotator cuff [58]. Kryger *et al.* compared mesenchymal stromal cells derived from bone marrow and from adipose tissue and found that both types of cells had similar properties *in vivo* and *in vitro*, but adipose-derived MSCs could proliferate faster in cell culture [59]. Small animal studies suggest that after transplantation, MSCs display the phenotypic characteristics of the endogenous surrounding tissue and may be an effective treatment for ligament injury [60-62].

Cell therapy with MSCs was more successful than with chondrocytes in native bone-tendon junction repair in a degenerative rat model [63]. In contrast, Gulotta *et al.* performed a controlled laboratory study using the transplantation of MSCs in a fibrin carrier into the supraspinatus tendon and found no differences in the amount of new cartilage formation or collagen fiber organization as well as no differences in the biomechanical strength of the repairs, the cross-sectional area, the peak stress to failure, or the stiffness despite confirmation of the presence and metabolic activity of the MSCs [64]. Another advantage of MSCs is their easy genetic manipulation. Adenoviral transduced MSCs with membrane type 1 matrix metalloproteinase [65] or with scleraxis [66] improved rotator cuff healing. MSCs in a fibrin glue also enhanced tendon graft osteointegration of the anterior cruciate ligament [67], and when transplanted into a bone tunnel improved the insertion healing of tendon to bone in a rabbit model through the formation of fibrocartilagenous attachment at early time points [68].

While the administration of MSCs alone appears to provide benefits for hematopoietic, neuronal and cardiac diseases, tendon repair often requires the structural and mechanical support provided by a scaffold. Collagen, laminin and fibrin are effective supports for MSCs in the initial stages of tendon injury repair [69-72].

Collagen gels were seeded with rabbit bone marrow-derived mesenchymal stem cells (MSCs) and contracted onto sutures at initial cell densities of 1, 4, and 8 million cells/ml. These MSC-collagen composites were then implanted into full thickness, full length, central defects created in the patellar tendons of the animal donors of the cells. These autologous repairs were compared to the natural repair of identical defects on the contralateral side. The results showed that surgical implantation of the tissue engineered MSC-collagen composites significantly improved the biomechanical properties of the tendon repair tissues, although greater MSC concentrations produced no additional significant histological or biomechanical improvement [73].

A variety of different carriers such as type I collagen gels [72], collagen sponges [74] and fibrin [75] have been used in animal models to deliver MSCs to the Achilles, patellar or rotator cuff tendons.

Our recent unpublished results showed that human MSCs when implanted to the rat Achilles tendon injury increase the amount of collagen I and III and neovascularization in the site of injury.

## 5. PHARMACOLOGY OF MSCS

In order to utilize MSC treatment in clinical trials, the conditions imposed by the European Medical Agency should be met regarding adequate preclinical supporting data. Although there have already been a number of animal experiments and even clinical trials and case reports with MSCs, only a small number of them can be utilized in the Investigator Brochure as supporting the safety and/or efficacy of MSC treatment. Three important aspects of the experimental work should be considered to support future clinical trial submission: similarity of methodology (especially the cell harvesting and *in vitro* expansion procedures), statistical quality (relevant number of subjects and validity of results), and cell characterization (panel of FACS-analysed surface antigens and if the differentiation of the cells was verified).

The acute systemic toxicity of allogeneic MSCs was studied in gamma irradiated rats [76]; there were no significant differences between test animals and controls regarding the presence of respiratory distress upon infusion, clinical assessment, haematology and clinical chemistry analysis after administration of *in vitro* expanded MSCs. Gross necropsy and histopathological analysis showed no organ profile alterations. There was no significant evidence for allogeneic antibody production or T-cell sensi-

tization upon MSC infusion. Although the article does not specify the details of cell characterization, the company description of MultiStem<sup>®</sup> (multipotent adult progenitor cells) includes plastic adherence, multipotency and positivity for CD105, CD73 and CD90 and negativity for CD45 and CD34.

The biodistribution of MSCs after systemic application is an important aspect to be considered for future clinical use. In order to transfer experimental data to the clinic, relevant tracking models for the cells should be constructed, such models include labelling the cells (immunolabeling, membrane soluble dyes, gene transfer) or utilizing non-autologous cells, such as human cells transplanted into an animal or allogeneic cells from an animal of the opposite sex and staining for the Y chromosome. An example of a MSC biodistribution study was published by Ezquer [77], in which the authors found systemically implanted MSCs in the bone marrow, kidneys and heart. Data on the migration and biodistribution of autologous MSCs in humans have not yet been published; however, the distribution of a similar cell type, bone marrow mononuclear cells (BMMCs), was analysed after intravenous injection [78]. Whole body scintigraphies indicated cell homing to the brain of all patients with a chronic ischemic stroke at 2 h post-infarct, while the remaining uptake was mainly distributed to the liver (44%), lungs (9%), spleen (4%), kidneys (4%) and bladder (9%). Moreover, quantification of uptake using Single-Photon Emission Computed Tomography (SPECT) at 2 h post-infarct showed the preferential accumulation of radioactivity in the hemisphere affected by the ischemic infarct in all patients. However, at 24 h homing could only be distinguished in the brains of 2 patients, while in all patients uptake was still seen in the other organs.

Despite many therapeutic benefits, MSCs have various adverse effects, mainly oncological. It was shown under experimental conditions that MSCs, when injected together with tumor cells, supported the growth of the tumor cells [79]. MSCs have been related to the promotion of metastasis [80] and play a role in the drug resistance of various cancer cells [81]. The immunosuppressive effect of MSCs encourages tumor growth, MSCs migrate to the tumor stroma, and promotes the angiogenesis, migration, invasion and metastasis of tumors [82]. The malignant transformation of MSCs when expanded *in vitro* has also been reported due to chromosomal instability in long-term culture [83]. Genetic modulation of MSCs can increase their oncogenic potential [84].

## 6. CLINICAL STUDIES

Despite the promising MSC-mediated effects on tendon healing noted in a number of animal studies, only a few clinical stem cell studies have been reported. Orthopaedic

dic stem cell studies in humans have predominantly focused upon enhancing bone healing, particularly in the spine, foot and ankle, and fracture surgery. Centeno *et al.* treated 227 patients with autologous MSCs that were cultured and then injected into peripheral joints ( $n = 213$ ) or intervertebral discs ( $n = 13$ ) [85]. The patients underwent disease surveillance for an average of 10.6 months, and no malignant transformations were reported. One patient was diagnosed with cancer which the authors believe was “certainly unrelated” to the MSC therapy. Seven patients had complications related to the injection, and 3 possible stem-cell-related complications were reported. Forty-five of the patients had serial MRIs for up to 2 years, and none of the patients showed any evidence of tumor formation, suggesting that MSC therapy is a relatively safe and well-tolerated procedure.

A pilot study enrolled 14 patients with complete rotator cuff tears repaired with transosseous stitches through miniopen incisions. Prior to cuff repair, autologous bone marrow mononuclear cells (BMMCs) were harvested from the iliac crest and subsequently injected into the repaired tendon borders [86]. The BMMC fractions were obtained by cell sorting and resuspended in saline enriched with 10% autologous serum. These patients were monitored for a minimum of 12 months, and their University of California, Los Angeles scores improved on average from  $12 \pm 3.0$  to  $31 \pm 3.2$ , and tendon integrity was demonstrated by magnetic resonance imaging in all 14 patients. No control group was included in this study, but historically for this procedure, overall rates of rerupture during the first postoperative year range from 25% to 65%, depending on lesion extent. Unfortunately, only 14 patients were enrolled in this study, making it difficult to determine the efficacy of BMMCs as an adjunct to cuff repair at this time. However, the implantation of BMMCs in RC tendon borders appears to be a safe and promising approach to enhance the efficacy of tendon repair.

Besides MSCs, other cellular therapies have been shown to clinically improve tendon healing. Clarke *et al.* applied skin-derived tenocyte-like cells to 33 patients with patellar tendinopathy and compared them to 27 patients who were treated with plasma [87]. The group receiving stem cell treatment noted a significant improvement in

Victorian Institute of Sport Assessment (VISA) scores. While both the cell and plasma groups showed an improvement in tendon hypoechoogenicity on ultrasound and tear size, only the cell group showed a significant decrease in tendon thickness.

A pilot study of 12 patients with refractory elbow epicondylitis treated with collagen producing cells derived from dermal fibroblasts showed a significant improvement in the patient-rated tennis elbow evaluation scale and ultrasound tendon appearance [88].

Mazzocca *et al.* used connective tissue progenitor cells (CTP) for rotator cuff repair in 23 patients and 23 controls. In the study, a standardized protocol for utilizing CTP and a potential positive therapeutic effect to enhance the rotator cuff healing process have been presented [89]. Results of the clinical studies are summarized in **Table 1**.

## 7. SUMMARY

Recent data provide extensive information about utilizing mesenchymal stem cells in regenerative medicine. Regarding tendons, the application of MSCs increase collagen fiber density, enhance tissue architecture and increase biomechanical strength. Due to the mesenchymal origin of these cells, they have been used to facilitate tendon tissue regeneration, but several questions concerning the clinical use of MSCs have been raised. Safety concerns about the use of mesenchymal stem cells in terms of their immunosuppressive effect, their possible genetic transformation and their manufacture for clinical use (expansion, phenotype and genetic stability in culture, cryopreservation and banking, microbial contamination) should be carefully considered [90]. In the face of many promising experimental and preclinical results, additional questions regarding the role of MSCs in the tendon healing process need to be addressed in order to achieve a better understanding of native tendon healing, the signal pathways for inducing tissue regeneration, and the molecular signaling for MSC differentiation. An interdisciplinary approach, including basic research in biology, bioengineering and clinical research, is required to achieve the successful clinical transfer of MSC treatment in tendon regeneration.

**Table 1.** Clinical studies.

Clinical studies		
Authors	Treatment	Results
Centeno <i>et al.</i> 2010	MSCs	Confirm the safety of the MSCs implantation
Ellera Gomes <i>et al.</i> 2012	BMMCs	MSCs is safe approach to treat tendon disorders
Clarke <i>et al.</i> 2011	Tenocyte-like cells derived from skin	VISA score was significantly improved
Connell <i>et al.</i> 2009	Tenocyte-like cells derived from skin	Significant improvement in ultrasound appearance
Mazzocca <i>et al.</i> 2010	Connective tissue progenitor cells	Positive therapeutic effect

## 8. ACKNOWLEDGEMENTS

This work was supported by the grant GAČR, P304/10/0326.

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