

# Current Evidence of Mesenchymal Stem Cells Use in the Treatment of Tendon Disorders: A Systematic Review, Meta-analysis, and Meta-regression of Prospective Clinical Studies

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## Research

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## Abstract

**Purpose:** Although several studies with animals have reported the effects of mesenchymal stem cells (MSCs) for tendon regeneration, little is known about the efficacy and safety of MSCs in human tendon disorders. We performed this meta-analysis to evaluate the efficacy and safety of MSC therapy in patients with tendon disorders enrolled in prospective clinical studies.

**Methods:** We systematically searched prospective clinical studies investigating the effects of MSCs administration on human tendon disorders with at least a 6-month follow-up period on PubMed-Medline, Embase, and Cochrane Library databases. The primary outcome of interest was the change in pain on motion related to tendon disorders. We performed a pairwise meta-analysis using the fixed-effects model to assess treatment response, which was calculated by the standardized mean difference. Meta-regression analyses were performed to assess the relationship between MSCs dose and pooled effect sizes in each cell dose.

**Results:** Four prospective clinical trials investigating the effect of MSCs on tendon disorders were retrieved. MSCs showed significant pooled effect size (overall Hedge's *g* pooled standardized mean difference (SMD) = 1.868; 95% confidence interval [CI], 1.274–2.462;  $P < 0.001$ ). The treatment with MSCs improved all the aspects analyzed, i.e. pain, functional scores, radiologic parameters (magnetic resonance image or ultrasonography), and arthroscopic findings. In the meta-regression analysis, there was a significant cell dose-dependent response in pain relief ( $Q = 9.06$ ,  $P = 0.029$ ). While three studies reported mild adverse events after MSCs injection, these were not severe and relieved spontaneously.

**Conclusions:** Our meta-analysis revealed that MSC therapy may improve pain, function, radiologic, and arthroscopic parameters in patients with tendon disorders. Due to the small number of studies in this meta-analysis and considering the increasing MSCs applications, there is a strong need for large-scale randomized controlled trials to confirm the long-term functional improvement as well as the adverse effects of MSC therapies in tendon disorders.

## Background

Mesenchymal stem cells (MSCs) treatment is a new regenerative therapy for treating tendon disorder. Preclinical studies have reported that MSC therapy may increase the number of tenocytes and regenerate the injured tendon tissue [1–4]. While several studies with animals support the treatment of tendon disorders using MSCs, little is known about the efficacy and safety of MSCs to treat these conditions in humans. Although a few clinical reports suggested the therapeutic potentials of MSCs in tendon disorders, they are mostly case reports or case series. Only one randomized controlled trial reported preliminary results (EudraCT Number: 2007-007630-19), but there are no published results yet [5].

A systematic review of MSC therapy on tendon disorder [6] analyzed three case series [7–9] and one matched non-randomized trial [10]. They concluded that MSC treatment is not yet suitable for clinical practice, because the included studies are at high risk of bias. However, the result should be reconsidered, since three [7, 8, 10] of the four studies included in this review were not performed with isolated MSCs but bone marrow aspirates or stromal vascular fractions cells. Moreover, this study was not carried out with the meta-analysis methodology, which combines the results from multiple studies. Furthermore, two current clinical studies [5, 11], which used isolated MSCs on tendon disorder, were not included in the review.

Although there is an increasing number of published research on stem cell treatments, there are no meta-analyses on this topic to date. Furthermore, concerns regarding possible adverse events of MSC treatments, raised by physicians or scientists reluctant to the therapy [12], should be thoroughly reviewed. Thus, we performed an updated meta-analysis of prospective clinical studies in order to evaluate the efficacy and safety of MSC therapies in patients with tendon disorder.

## Methods

### Search Strategy

The meta-analysis was conducted according to the updated guidelines of the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) [13]. Searches on PubMed-Medline, Embase, and Cochrane Library were performed in February 2019 using the following key terms and syntax: (Tendinopathy OR Tendon OR Tendon disorder OR Tendon injuries OR Tendinosis OR Tendinitis OR Tennis elbow OR Elbow Tendinopathy OR Lateral epicondylitis OR Lateral epicondylosis OR Golfer's elbow OR Rotator cuff OR Rotator Cuff Injuries OR De Quervain disease OR Jumper's knee OR Achilles tendon) AND (Stem cells OR Mesenchymal stem cells OR Progenitor cells OR Mother cells OR Multipotent OR Pluripotent OR Totipotent) AND Clinical studies [14, 15]. An overview of the search strategy is presented in Supplementary Appendix A. We included all prospective clinical studies investigating the effects of MSCs administration on tendon disorder. We imposed no language restriction. We also searched for unpublished and grey literature using the following databases and trial registries: World Health Organization Clinical Trial Register, EU clinical trials register, ClinicalTrials.gov, and OpenGrey.

### Study Selection Criteria

Identified records were saved to the EndNote software (X7.2; Thomson Reuters). Two independent reviewers (WSC and SYL) screened all the titles and abstracts to identify relevant investigations. The inclusion criteria were as follows: (1) articles reporting a prospective clinical study with at least a 6-month follow-up that (2) described the effect of MSC therapy in patients with any tendon disorder. Although there were no limitations in types of MSCs, i.e. cell origin; autologous or allogeneic, we excluded studies which did not use isolated MSCs, e.g. bone marrow aspirates or stromal vascular fractions cells. Reviews, basic science articles, comments, letters, and protocols were excluded. When updates of earlier studies were available, we used only the most recent ones.

## Outcome Measures and Data Extraction

The primary outcome of interest was defined as pain on motion related to tendon disorder. All types of pain measurements, e.g. visual analog scale or numeric rating scale, were included. The secondary outcomes analyzed in this study were as follows: 1) functional scores of joint, such as the Constant score, the UCLA score, the modified Mayo elbow performance index, or the Shoulder Pain and Disability Index; 2) radiological parameters to measure tendon defects using magnetic resonance image or ultrasonography; and 3) arthroscopic findings to measure tendon defects with a calibrated arthroscopic probe. For every eligible study, the following data were extracted and entered into a spreadsheet by the two reviewers (WSC and SYL): first author's family name, year of publication, study design, types of tendon disorder, origin of the MSCs, number of patients, MSCs injection methods, cell doses, follow-up duration, safety assessment, and efficacy measurements. We assessed publication bias using Begg's funnel plot [16] and Egger's test [17].

## Statistical Analysis

Effect sizes were computed as standardized mean difference (SMD) measures,[18] representing the magnitude of the pretest-posttest difference for each outcome. SMD was calculated separately for all the available control and treatment groups for each study. Heterogeneity between comparable studies was tested with the chi-squared ( $\chi^2$ ) and  $I^2$  tests. Values of  $P > 0.1$  and  $I^2 < 50\%$  were considered statistically significant. Because there was no significant heterogeneity among the four studies ( $P = 0.658$  and  $I^2 = 0.0\%$ ), we used a fixed-effects meta-analysis to quantify the pooled effect size of the studies included. In each analysis by outcome, the following parameters: pain ( $P = 0.093$  and  $I^2 = 47.0\%$ ), functional scores ( $P = 0.313$  and  $I^2 = 15.3\%$ ), radiological parameters ( $P = 0.406$  and  $I^2 = 0.0\%$ ), and arthroscopic findings ( $P = 0.588$  and  $I^2 = 0.0\%$ ) were also analyzed using the fixed-effects model. Additionally, we performed a meta-regression analysis to assess the relationship between MSCs dose and pooled effect sizes in each cell dose. All analyses were performed using the Comprehensive Meta-Analysis Software (version 3.3; Biostat, Englewood, NJ, USA). This study was exempted from Institutional Review Board review as no human subjects were involved.

## Results

### Description of Included Studies

The primary database search yielded 1,135 records. After duplicates were removed, the titles and abstracts of 897 articles were initially screened and 25 selected for full-text review. The full-text articles were read and 4 were considered relevant by qualitative analysis [5, 9, 11, 19]. The studies selected for inclusion or exclusion are shown in Fig. 1, and the characteristics of the included studies are summarized in Table 1. In terms of quantitative analysis, these four studies (published from 2015 to 2018) fulfilled our inclusion criteria. Three papers [9, 11, 19] were open-label prospective studies, while one [5] was an unpublished double-blind randomized controlled trial. The studies identified for meta-analysis included 52 participants. Two studies [9, 19] employed adipose tissue-derived MSCs and the other two [5, 11] administered bone marrow-derived MSCs. The number of cells used in each study ranges from  $10^6$  to a maximum of  $10^8$ . Regarding tendon disorder types, most of the studies were performed on rotator cuff tear, but one study [9] was conducted on lateral epicondylitis. The follow-up duration ranged from 6 to 12 months.

**Table 1. Characteristics of the Individual Studies Included**

Study	Region	Study period	Study design	N	Tendon disorder	MSC origin (type)	Injection method	MSC dose (cells)	F/U period	Safety	Efficacy	
											Primary	Secondary
Jo 2018	South Korea	Jul 2015 - Nov 2016	Open-label, dose-escalation trial	19	Partial-thickness rotator cuff tear	Autologous adipose tissue-derived MSCs	Intratendinous injection under the US guidance, MSCs in 3 ml of saline	$1.0 \times 10^7$ , $5.0 \times 10^7$ , $1.0 \times 10^8$	6 mo	NCI-CTCAE v 4.0	SPADI	Constant score, pain (VAS) shoulder MRI (tendon defects), arthroscopy
Lee 2015	South Korea	May 2013 - Sep 2014	Open-label, conventional 3+3 cohort expansion design	12	Lateral epicondylitis	Allogeneic adipose tissue-derived MSCs	Intratendinous injection under the US guidance, MSCs with fibrin glue (total volume of 1 ml)	$1.0 \times 10^6$ , $1.0 \times 10^7$	12 mo	Local/systemic tolerances, US exam	Pain (VAS)	Modified mayo elbow performance index, elbow US (tendon defects)
Havlas 2015	Czech Republic	Oct 2012	Prospective study with consecutive participants	8	Rotator cuff tear	Autologous bone marrow-derived MSCs	Arthroscopic repair and suspension of MSCs to the suture site	$1.0 \pm 0.45 \times 10^7$	6 mo	Local and systematic adverse reactions (not clearly described)	Pain (VAS)	Constant score, UCLA score
Lamas 2015	Spain	Apr 2010	Double-blind randomized controlled trial	13	Full-thickness rotator cuff tear	Autologous bone marrow-derived MSCs	Surgical repair with Attached with OrthADAPT™ membrane	$2.0 \times 10^7$	12 mo	Examined but not mentioned	Constant score	Tendon status by MRI Pain (VAS)

*Abbreviations:* MSCs, Mesenchymal Stem Cells; US, Ultrasonography; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events; SPADI, Shoulder Pain and Disability Index; VAS, Visual Analog Scale; MRI, Magnetic Resonance Imaging; UCLA, University of California at Los Angeles.

## Results after Analysis and Publication Bias

The MSC therapies showed a significant pooled effect size (overall Hedge's *g* pooled SMD = 1.868; 95% confidence interval [CI], 1.274–2.462; *P* < 0.001) (Fig. 2). The parameters of pain, functional scores, radiological parameters (magnetic resonance image or ultrasonography), and arthroscopic findings all improved with MSC treatment (Fig. 3). In the meta-regression analysis, there was a significant cell dose-dependent responses in pain relief (*Q* = 9.06, *P* = 0.029) (Fig. 4). While three studies reported mild adverse events after MSCs injection, these were not severe and relieved spontaneously (Table 2). Publication bias was not evident, as shown by the symmetrical Begg's funnel plot (Supplementary Appendix B), and the *P*-value for bias was 0.625 (Egger's test; all four trials).

**Table 2. Adverse Events Reported in Individual Studies Included**

Study	Adverse events	N	Treatment	Prognosis	Treatment-related
Jo 2018	Back pain	3	Rescue drug, physical therapy	Recovered	No
	Right foot bruise, left trigger finger	1	Rescue drug, physical therapy	Recovered	No
	Cough	1	Medication	Recovered	No
	Left eye pain	1	Eye drop	Recovered	No
	Abdominal pain	1	Medication	Recovered	No
Lee 2015	Mild regional swelling	6	Observation	Recovered	Yes
	Mild elbow joint effusion	2	Observation	Recovered	Yes
	Delayed elbow pain	1	Rescue drug	Recovered	No
Lamas 2015	Swelling, pain, reduced range of motion (chronic synovitis)	4	Surgery (remove the patch)	Recovered	Yes

## Discussion

Potential evidence has shown that the MSCs injection improves pain, joint functions, radiological, and arthroscopic parameters in patients with tendon disorder. Although all included studies had a small sample size, the results clearly presented MSCs dose-dependent responses regarding pain relief. To the best of our knowledge, this is the first clinical meta-analysis describing the pooled effects of MSC therapies on patients with tendon disorder.

Tendon injuries are a common health problem, which are defined as a painful condition occurring around tendons that limits the function of the affected tendons [20]. Tendons are susceptible to repeated use or degenerative condition. Injuries in those structures are rarely regenerated but repaired by scar tissue and fibrosis. This healed tissue presents inferior tensile strength and is prone to further injuries. Preclinical studies support that MSCs have a regenerative potential as those cells are able to differentiate into proper tendon cell and elicit the secretion of cytokines or growth factors [1]. Therefore, MSCs have been regarded as a possible curative treatment option for tendon degeneration.

Implanted stem cells survive in tendon defects, differentiate into the tenogenic cell lineage and secrete their own extracellular matrix to promote tendon healing [4]. Mazzocca et al. showed that bone marrow-derived stem cells differentiate into tendon-like cells [21]. Lee et al. also reported that transplanted human adipose tissue-derived stem cells survived for at least 4 weeks in the rat tendon injury model and released human-specific collagen type I and tenascin-C (TnC) [4]. The expression of TnC is known to increase rapidly during the early period of recovery after tendon injuries, and thus may be used as a marker of tenogenic differentiation [22].

In this meta-analysis, three of the four included studies examined radiological data (magnetic resonance image or ultrasonography) or arthroscopic findings after MSCs injections. These tests could confirm that the injected cells not only relieved pain and improved functions but also regenerated the damaged tissue. Noteworthy, Jo et al conducted the second-look arthroscopic examination at 6 months following MSCs injection as well as MRI follow-up [19]. They reported that the regenerated tendon tissues were identified in all subjects regardless of the location and size of the tear. The defect volumes were decreased in the groups that received mid-dose ( $5.0 \times 10^7$  cells) and high-dose ( $1.0 \times 10^8$  cells). Although this is a macroscopic observation, it may be strong supporting evidence for the regeneration effect of MSCs.

Another important biological mechanism supporting MSC therapy is paracrine effect exerted by these cells [1]. Kinnaird et al. found that growth of endothelial cells and smooth muscle cells may be promoted by the use of medium conditioned with MSCs. This phenomenon might be partly explained by the presence of VEGF and bFGF, which appeared in high levels in the MSCs conditioned medium [23]. The ability of the MSCs to produce a wide range of immunomodulatory and trophic factors has also attracted great attention [24].

There are several concerns regarding the use of MSCs as a treatment option for tendon disorder. Particularly, potential long-term adverse events from the stem cell treatment have been poorly reported in several clinical studies. In the studies included in this meta-analysis, most of the reported adverse events were not related to treatment (Table 2). The treatment-related side effects were regional swelling following allogeneic stem cell injection [9] or engrafted patch-related chronic synovitis [5]. The joint swelling spontaneously subsided, while the patch-related adverse event needed additional surgery. Considering the prognosis of the reported adverse events, these side effects might have come from the localized inflammatory response related to the treatment procedure, or to immunologic response against allogeneic cells.

The safety issues related to the MSCs have already been sufficiently assessed in clinical trials in the field of internal medicine, in which MSCs are injected systemically. The POSEIDON trial [25] was designed to investigate the safety and efficacy of autologous and allogeneic MSC therapies for ischemic

cardiomyopathy. The study reported that, following trans-endocardial stem cell injection, the treated group showed improvement in structural and functional outcomes, while no serious adverse events including immunologic reactions occurred. Indeed, long-term adverse events from the stem cell treatment and its possible teratogenicity should be thoroughly considered. One animal study reported undesired cartilage formation after the injection of human MSC in eighty-one rat tendon injury models [26]. While there was no histologic evidence of tumor formation in the study, concerns for possible teratogenicity still remain.

Although there are numerous challenges to be overcome and analyzed, it is undisputable that MSC therapy is a potential treatment option to treat tendon disorder. In particular, about 17% of patients with tendon disorder are known to have no effects after undergoing conservative treatment for more than one year [27]. In some patients, the rate of re-tear is fairly high, even following surgical repair for tendon injuries [19]. Thus, the limitations of the current therapies suggest a need for more fundamental regenerative treatments and MSCs might offer the regenerating opportunity for the tendon by yielding a more robust repair tissue [28]. In order for MSCs injections to be established in tendon disorder, the aforementioned long-term safety issues should be better verified. Furthermore, well-designed clinical trials should be performed in order to support the evidence.

There are several limitations to this meta-analysis. First, we employed a limited number of studies included in our meta-analysis. Moreover, there was only one randomized controlled study available, which has not been published yet. Since MSCs have been applied for the treatment of tendon disorder for only a short period of time, the number of studies that fulfilled our criteria was limited. If a sufficient number of studies had been analyzed, more solid evidence could have been obtained. However, it is meaningful to combine the data through the meta-analysis because there are not enough studies related. Second, included studies were heterogeneous in many ways. Two studies were performed with the administration of bone marrow-derived MSCs, while the other two studies used adipose tissue-derived MSCs. The specific disease entities presented in the studies were also different, namely three studies aimed at treating the rotator cuff disease and one, lateral epicondylitis. However, in order to assure that the mechanisms and efficacy of MSC therapies in tendon disorder are clear and evident, it will be necessary to evaluate whether these treatments are suitable for not just a single specific tendinopathy but for multiple pathologies, which may involve various musculoskeletal structure.

## Conclusions

Our meta-analysis revealed that MSC therapy may improve pain, function, and radiological and arthroscopic parameters in patients with tendon disorder. Due to the limited sample size in this meta-analysis and considering the increasing MSCs applications, there is a strong need for large-scale randomized controlled trials to confirm the long-term functional improvement and adverse effects of MSC therapies in tendon disorder.

## List Of Abbreviations

MRI: magnetic resonance image; MSCs: mesenchymal stem cells; PRISMA-P: Preferred Reporting Items for Systematic review and Meta-Analysis Protocols; SMD: standardized mean difference; TnC: tenascin-C

## Declarations

**Ethics approval and consent to participate:** Not applicable

**Consent for publication:** Not applicable

**Availability of data and materials**

All data generated or analysed during this study are included in this published article and its supplementary information files.

**Competing interests:** The authors declare that they have no competing interests.

**Funding:** None.

**Authors' contributions**

WSC, SGC and SYL designed the study. WSC and SYL collected the data. WK and SYL conducted the data analysis. CHJ, SUL and SYL interpreted results and drafted the manuscript. All authors read and approved the final manuscript.

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## Figures

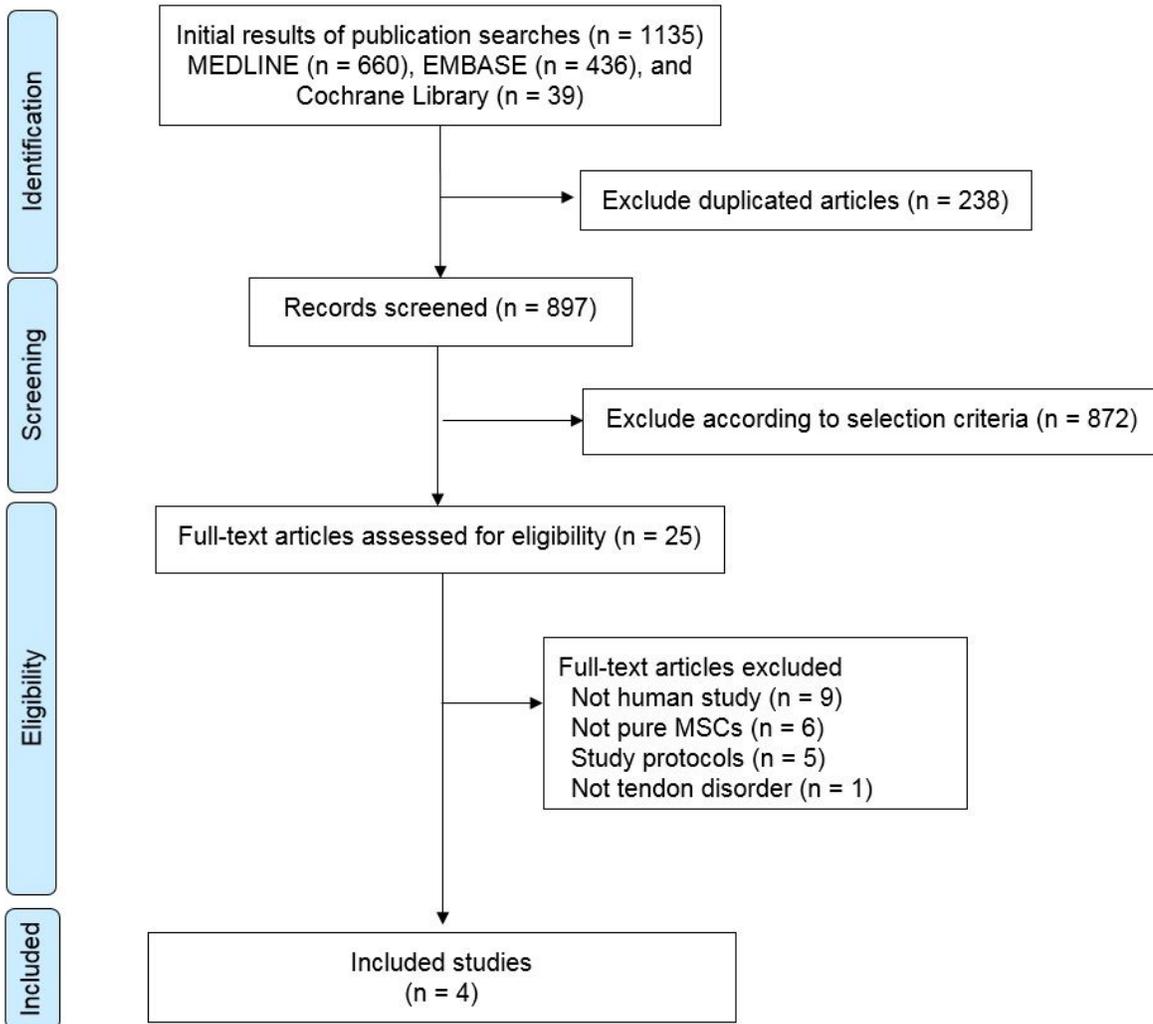


Figure 1

Preferred Reporting Items for Systematic review and Meta-Analysis flow diagram detailing the selection process of relevant clinical studies.

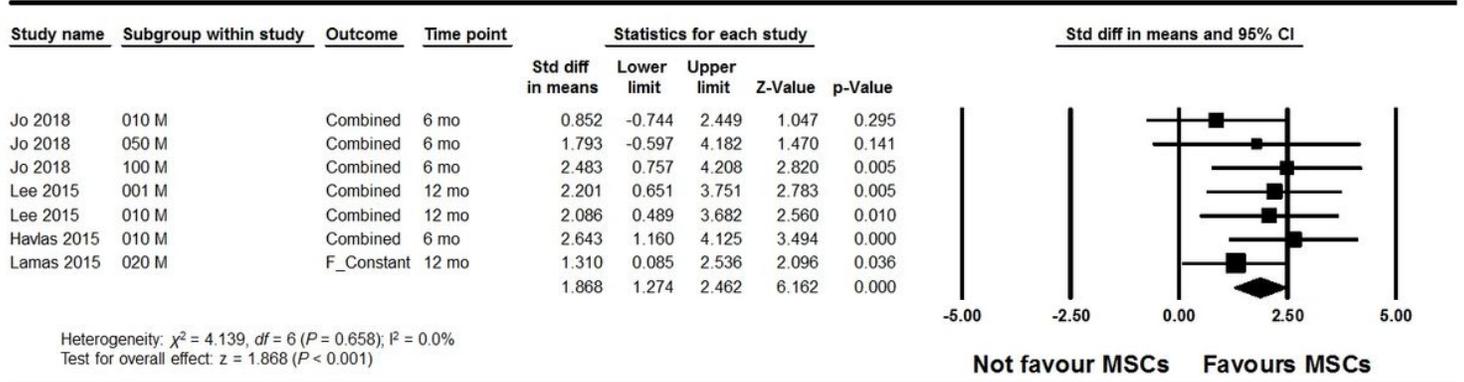
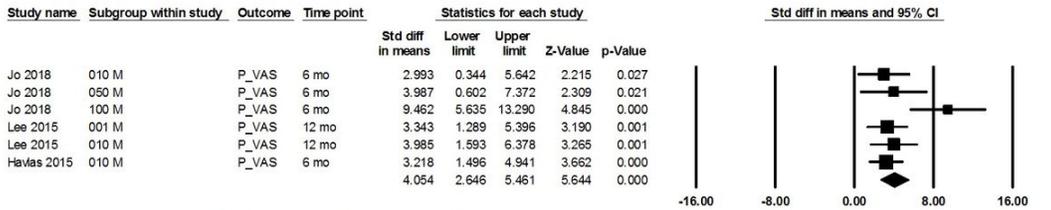


Figure 2

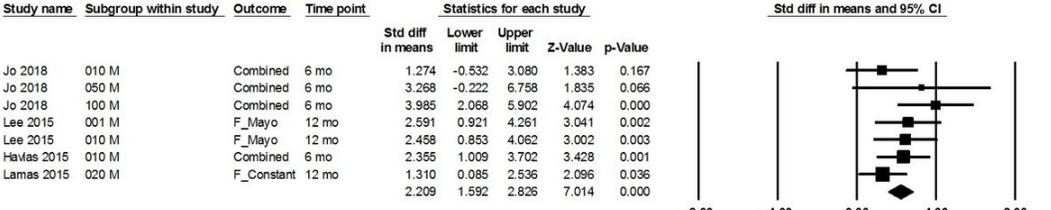
Forest plot of the pooled effect of MSCs on tendon disorders determined by a fixed-effects meta-analysis. Effect sizes are indicated as Hedges' g standardized mean differences and 95% confidence intervals.



Heterogeneity:  $\chi^2 = 9.425$ ,  $df = 5$  ( $P = 0.093$ );  $I^2 = 47.0\%$   
 Test for overall effect:  $z = 4.054$  ( $P < 0.001$ )

**(A) Pain**

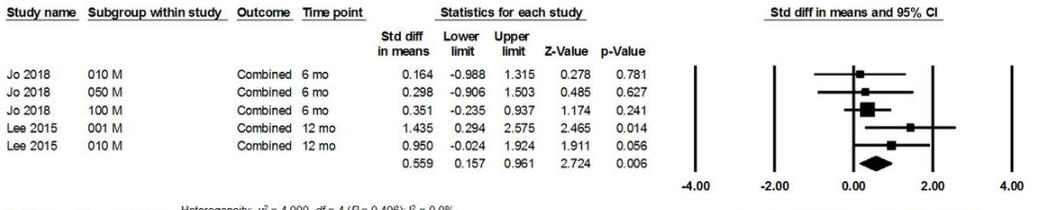
Not favour MSCs Favours MSCs



Heterogeneity:  $\chi^2 = 7.084$ ,  $df = 6$  ( $P = 0.3131$ );  $I^2 = 15.3\%$   
 Test for overall effect:  $z = 2.209$  ( $P < 0.001$ )

**(B) Function**

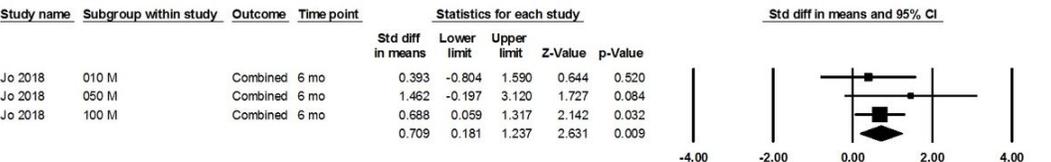
Not favour MSCs Favours MSCs



Heterogeneity:  $\chi^2 = 4.000$ ,  $df = 4$  ( $P = 0.406$ );  $I^2 = 0.0\%$   
 Test for overall effect:  $z = 0.559$  ( $P = 0.006$ )

**(C) Imaging study**

Not favour MSCs Favours MSCs



Heterogeneity:  $\chi^2 = 1.062$ ,  $df = 2$  ( $P = 0.588$ );  $I^2 = 0.0\%$   
 Test for overall effect:  $z = 0.709$  ( $P = 0.009$ )

**(D) Arthroscopy**

Not favour MSCs Favours MSCs

Figure 3

Forest plots of the effects of trial/cell dose-level characteristics of MSCs analyzed as outcome variables: (A) pain (primary outcome), (B) functional scores, (C) radiologic parameters, and (D) arthroscopic findings.

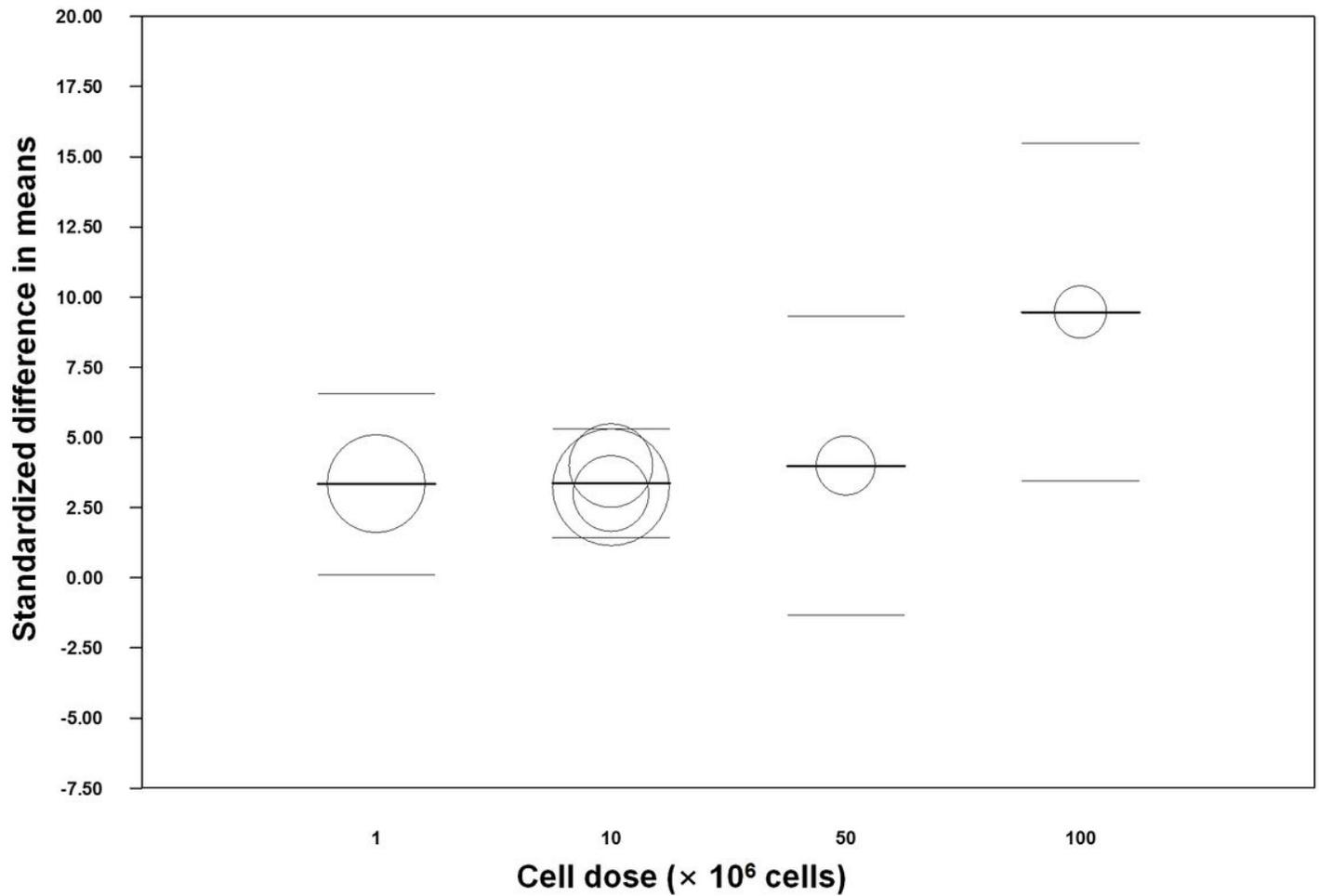


Figure 4

Meta-regression of the standardized mean differences in means for cell dose. The area of the circles is proportional to the studies' weights in the regression.

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [AppendixAQuery.docx](#)
- [AppendixB.Funnelplot.tif](#)