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The effect of regenerative therapy in functional outcome in the treatment of patellar and Achilles tendinopathy: A Meta-analysis of Randomized Controlled Clinical Trials

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Abstract

Background: *Achilles and patellar tendinopathy are the most common musculoskeletal disorders in lower extremities, with numerous therapeutic modalities for treatment and management. Nowadays, cell-based therapies like stem cells (SC) and platelet-rich plasma (PRP) have satisfactory clinical outcomes.*

Aim: *To perform a meta-analysis of randomized controlled clinical trials to determine the functional efficacy of cell therapy (SC or PRP) in patellar (PT) and Achilles tendinopathy (AT).*

Study Design: *Meta-analysis.*

Methods: *PubMed, Cochrane Library, Google Scholar, SciELO, International Clinical Trials Registry, Clinical Trials.gov, and Lilacs were searched from January 2010 to May 2021. Reference lists were manually checked. Randomized controlled trials (RCTs) using SC and PRP to treat tendinopathy using the Victorian Institute of Sport Assessment (VISA) for patellar (VISA-P) and Achilles (VISA-A) tendinopathy were included. Published RCTs using other treatment modalities, non-tendon condition, non-per-protocol analysis, and other studies designs were excluded. Study quality was assessed using the CONSORT 2010 checklist for reporting a randomized trial. The Cochrane Collaboration risk of bias tool for randomized trials was used, and two review authors assessed their quality. The effect size was reported as a standardized mean difference (SMD) in a random effect model. The sensitivity analysis for publication bias was evaluated. A funnel plot was used, and Egger´s regression test was performed for asymmetry evaluation.*

Results: *A total of eight RCTs with cell therapy were considered. The studies included a total of 318 patients with PT and AT with a mean follow-up of 28.75 (+-11.82) weeks. There was no significant difference between the two groups in the random-effects model (SMD=0.43, 95%CI (-0.52, 1.37), t=1.07, p=0.32). No significant difference between subgroups analysis considered the type of regenerative therapy (Q=3.49, df=2, p=0.17), and injection site (Q=0.36, df=1, p=0.55) were detected.*

Conclusion: *This meta-analysis does not provide enough evidence to support the use of cell therapy (SC and PRP) to manage PT and AT.*

Keywords: *Achilles, Patellar, Platelet-rich plasma, Tendinopathy, VISA.*

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INTRODUCTION

Tendinopathy is any tendon condition that is often near its insertion and is directly related to the volume of repetitive load (Xu, 2008). Patellar (PT) and Achilles (AT) tendinopathies are the most frequent knee and ankle and foot overuse injuries (Schwartz, 2015; Li, 2016). Especially in the athletic (Maffulli, 2003) and non-athletic populations (Tan, 2008; Andrew, 2014). It presents as pain in the affected area, with or without activities, dysfunction, tenderness, swelling, stiffness (Simpson, 2016), decreasing strength and flexibility of the segment (Bass, 2012), impacting on patients' quality of life and the cost-effectiveness of treatments (Hopkins, 2016).

The growing prevalence of both tendinopathies and their impact on the general public has prompted the development of numerous therapeutic and management modalities. Including non-operative interventions such as eccentric exercises, non-steroidal anti-inflammatory agents (NSAIDs), corticosteroids, nitric oxide, and operative interventions, for example, percutaneous longitudinal tenotomy, ultrasonic microtenotomy (Mead, 2018), and cell-based therapies to regenerate tendon tissues with satisfactory clinical outcomes (Ruzzini, 2012).

Regenerative therapies are the therapeutic application of cells such as stem cells (SC) or platelet-rich plasma (PRP) to stimulate repair mechanisms and restore function in damaged body tissues or organs (Liu, 2017; Costa-Almeida, 2019; Ntege, 2020). There exists a vast difference in their preparation procedures and their functionality. For example, SC is isolated from the adult tissues and cultured in sophisticated settings and requires several weeks to grow before it could be used for therapeutics. Contrary to SC, preparation of PRP is simple and involves rapid separation from blood and does not contain SCs for therapeutics per se (Ramaswamy, 2018) (**Figure 1**).

Recently, there is level 3 of evidence to support the efficacy of stem cell therapy for tendon disorders (van den Boom, 2020) and the use of PRP in the treatment of AT (Madhi, 2020). However, the authors of those articles concluded that the studies published on SC and PRP injections in treating tendinopathy have different preparation methods and interpretations of efficacy. Moreover, a recent systematic review of high-quality randomized controlled trials studied the efficacy of PRP injections for treating Achilles' tendinopathy and did not reveal a strong basis for supporting the premise that PRP treatment for this disorder with any clear clinical advantage over other treatment modalities (Wang, 2019). For patellar tendinopathy, in turn, one systematic review and meta-analysis of randomized injection-controlled trials reported only pain results without addressing any other relevant clinical outcomes (Miller, 2017).

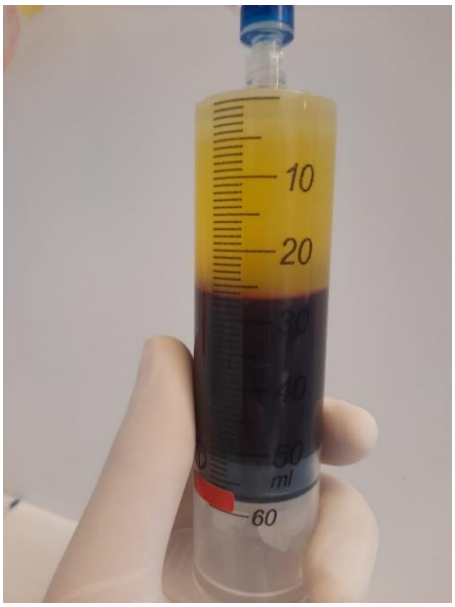

Figure 1. Platelet rich plasma preparation. The interface between red blood cells and plasma is visible in the picture after the first centrifugation in a two-step centrifugation protocol.

The current meta-analysis was done to assess the efficacy of regenerative therapy (SC and PRP) in functional outcomes in the treatment of PT and AT.

METHODS

Reporting

This article followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines (PRISMA, 2020). The PRISMA 2020 statement comprises a 27-item checklist addressing a systematic review report's introduction, methods, results, and discussion sections. The checklist is available in (Prisma-statement).

Research Question

The research question was to assess the efficacy of SC and PRP based on patient-reported functional outcomes using the Victorian Institute of Sport Assessment (VISA) for Patellar (VISA-P) (Visentini, 1998) and Achilles

(VISA-A) (Robinson, 2001) tendinopathy. The VISA(A/P) questionnaires have been recommended by the 2020 consensus statement (Vicenzino, 2020) and are the most used condition-specific lower limb questionnaires in the literature. Six out of eight items rate pain levels during daily activities and functional tests, and two items provide information on the impact of tendinopathy in physical activity or sports participation (Korakakis, 2021). The following PICOT (Participants, Interventions, Comparison, Outcome, and Time) criteria were used Table 1.

Selection criteria, patients, and interventions

The inclusion criteria were published studies, randomized clinical trials, tendinopathy diagnosis based on clinical examination or imaging (e.g., Magnetic resonance imaging and/or ultrasound), patient-reported functional scale (VISA, VISA-A, VISA-P), tendon healing, treatment with SC or PRP (any origin, dosage, volume, number of injections). All patients were adults (over18 years). Controls were any substance (placebo or injection).

Table 1. PICOT strategy for this study.

PICOT Acronym	PICOT Component	PICOT Component Explanation
(P)	Population	Patients over 18 years, regardless of gender, race, or ethnicity with a clinical diagnosis (imaging and functional tests) of PT or AT.
(I)	Intervention	Any dosage, volume, and frequency of SC or PRP injections US-guided or not, that have been assessed in clinical trials.
(C)	Comparison	Patients under standard therapy or persons under any other non-SC or PRP based therapy.
(O)	Outcome	The primary outcome was the change of functional outcome in the VISA for VISA-A and VISA-P.
(T)	Time	The follow up was 12 to 26 weeks.

PT: Patellar tendinopathy; AT: Achilles tendinopathy; SC: Stem cell; PRP: Platelet-rich plasma; US: Ultrasound; VISA: Victorian Institute of Sport Assessment; VISA-A: Victorian Institute of Sport Assessment- Achilles; VISA-P: Victorian Institute of Sport Assessment-Patellar.

The exclusion criteria were previous surgery, prosthesis, cancer diagnosis, dyslipidemia, thyroid disorder, chemo- or radiation therapy, or any hematologic condition.

These criteria were similar to the criteria previously used by another author (van den Boom, 2020).

Outcomes

The primary outcome was measured as a change in function using the VISA, VISA-A, VISA-P. We analyzed all articles with the final follow-up per protocol.

Search Strategy and Data sources

A systematic literature search was performed by two independent authors (G. D and A. S) using the following databases: MEDLINE/PubMed (https://www.ncbi.nlm.nih.gov/pubmed/), Cochrane Library (https://www.cochranelibrary.com/), SciELO (https://scielo.conicyt.cl/), International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/), Clinical Trial gov (https://clinicaltrials.gov/), Lilacs (https://lilacs.bvsalud.org/en/). Complementary sources such as Open Grey (http://www.opengrey.eu/), Web of Science (https://login.webofknowledge.com/), Google Scholar (https://scholar.google.com). The search was performed from January 2010 to May 2021.

The process of choosing the MeSH (medical subject headings) was using indexer keywords in the MeSH database available for free online: http://www.ncbi.nlm.nih.gov/mesh. Also, we used synonyms in tendinopathies such as tendinopathy, tendinitis, and tendinosis to guarantee included every keyword. Also, FA, a coauthor in this article, is an expert in regenerative therapy, and he works as Director in a Cell Therapy Laboratory. He validated the keywords

that were used in the article. Key search words included: Cell-therapy, stem-cell, platelet-rich plasma, tendinitis, tendinopathy, tendinosis, therapy, knee (patellar tendinopathy), ankle (Achilles tendinopathy).

The language was limited to English, Portuguese, and Spanish. The complete search strategy is contained in Appendix 1.

Study selection

Two authors (G.D and A. S) performed study selection using the selection criteria and keywords. They removed all duplicated articles. Any discrepancies in article selection were resolved by a third author (F. A).

Randomized clinical trials with outcome results were selected manually. Case reports and literature reviews were excluded. The methodological quality assessment for clinical trials was evaluated using the CONSORT statement and its corresponding checklist (http://www.consort-statement.org/).

A total of 956 articles were identified through the database and metasearch process (**Figure 2**). After applying filters, 106 articles were screened, and 52 were removed. Forty-six articles were excluded (non-per-protocol analysis, not RCTs, non-tendon condition). The number of full-text articles assessed for eligibility criteria was 54. Finally, eight articles were included for complete analysis.

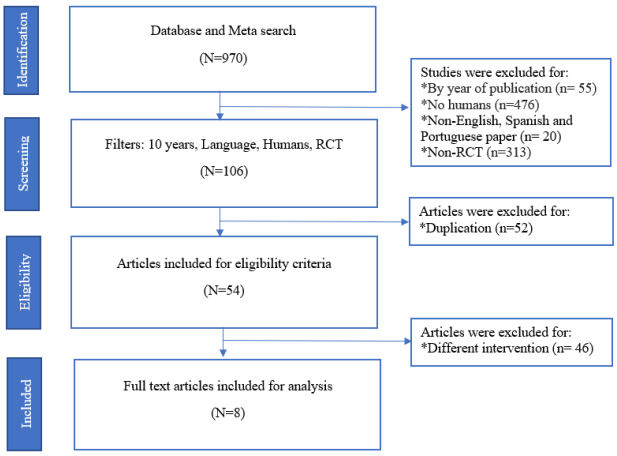

Figure 2. Flow diagram of selection process of patellar and Achilles's tendinopathy stem cell and platelet-rich-plasma therapy. RCT, Randomized clinical trial.

Data collection process

Two independent reviewers (G.D) and (A.S) have searched and applied both the selection criteria. Data extraction was done separately, and it was registered in an Excel spreadsheet (Microsoft Corp). Then, the information was collected for final review among the two reviewers for final agreement to be included and analyzed. The data extraction included mean and standard deviations, with 95% confidence intervals (CIs) from each article.

Ethical approval

All studies were in accordance with the Helsinki declaration and ethical committee board approval. Informed consent was obtained from all individual participants in each included study.

Risk of Bias Assessment

The critical appraisal was evaluated in all included RCTs. The Cochrane Collaboration risk of bias tool for randomized trials was used. We assessed the following factors:

1. Bias arising from the randomization process
2. Bias due to deviations from intended interventions
3. Bias due to missing outcome data
4. Bias in the measurement of the outcome
5. Bias in the selection of the reported result

These were given a rating of low, some concerns, or a high risk of Bias (Higgins, 2021).

Statistical analysis

Random-effects meta-analysis models were selected a priori for data analysis because this model assumes the observed treatment effect can vary across studies and the fundamental differences in the treatment effect in each study and sampling variability (chance) (Riley, 2011). The effect size data were recollected as continuous, unmatched groups, and post data were analyzed only with means, standard deviation, and sample size in each group. The difference between mean outcomes in the different intervention groups (Sullivan et at., 2012) was calculated. The effect size was reported as a standardized mean difference (SMD) (95% CI) or the Hedges´g (95% CI) (Higgins, 2021). This statistic is preferred to Cohen´s statistic because it has better properties when significantly different sample sizes. Hedge´s g interpretation is 0.2 for a small effect, 0.5 for a medium effect, and 0.8 for a large effect (NIST, 2018). Subgroups analysis was done to identify differences in cell therapy preparation and injection tendon site (Achilles or patellar). Additionally, forest plots were used to assess effect sizes graphically. The heterogeneity of treatment effects among studies

was measured with the I2 statistic (>50% is considered as having substantial heterogeneity). The sensitivity analysis for publication bias was evaluated. A funnel plot was performed to observe effect size on the x-axis against a measure of their standard error on the y-axis. To distinguish publication bias from other forms of asymmetry, we performed a contour-enhanced funnel plot to how asymmetry patterns relate to statistical significance. Egger´s regression test was used (Mathur, 2020) as a quantitative method to evaluate funnel plot asymmetry.

A two-sided significance level of <0.05 was considered. All statistical analyses were performed using the R (v 4.1.0) software package.

RESULTS

For this meta-analysis, we selected eight RCTs, including a total of 318 participants with patellar or Achilles tendinopathy: (Clarke, 2010), (de Vos, 2010), (Vetrano, 2013), (Kearney, 2013), (Dragoo, 2014), (Krogh, 2016), (Boesen,2017), (Thermann, 2020). Each RCT had been registered with clinicaltrials.gov with a serial number (clinicaltrial.gov). Five of the eight studies were categorized at the highest of evidence (level 1). The range of age for all patients was 18 to 70 years. The preparation of SC therapy or PRP injections, as well as the doses used, was different within the intervention group (over100 patients), with a mean follow-up of 28.75 (+-11.82) weeks (Table 2).

Risk of bias in the selected studies

The risk of bias was evaluated within each selected article. **Figure 3** shows the eight studies assessed based on the risk of bias. No article got five dimensions of assessment with a low risk of bias. Dimensions one and four presented three risks of bias with some concerns. Moreover, dimension three got three articles with a high risk of bias. Three publications presented overall the best score in the risk of bias evaluation (Clarke, 2010; Vetrano, 2013; Thermann, 2020)

Network Meta-analysis

All eight studies evaluated the VISA score. Three studies used the VISA-P, and the rest of the studies applied the VISA-A scores – which is a strong advantage compared to other meta-analysis reports and systematic reviews – in similar cut point periods.

Studies were analyzed using two criteria, one group as an experimental and the other as a control. We identified at least three active interventions using an intratendinous injection. One study applied Skin-derived tendon-like cells injection (Clarke, 2010).

Three articles used GPS II and III platelet separation systems (BiomeT) (de Vos, 2010, Dragoo, 2014, and Krogh, 2016). One author reported a GenesisCS (Kearney, 2013). Those systems reportedly produce Leukocyte Rich Platelet Rich Plasma (LR-PRP), but one investigator explicitly reported that it was (Dragoo, 2014). The remaining authors used PRP kit systems that produce Leukocyte Poor Platelet Rich Plasma (LP-PRP) (Vetrano, 2013; Boesen 2017; Thermann, 2020).

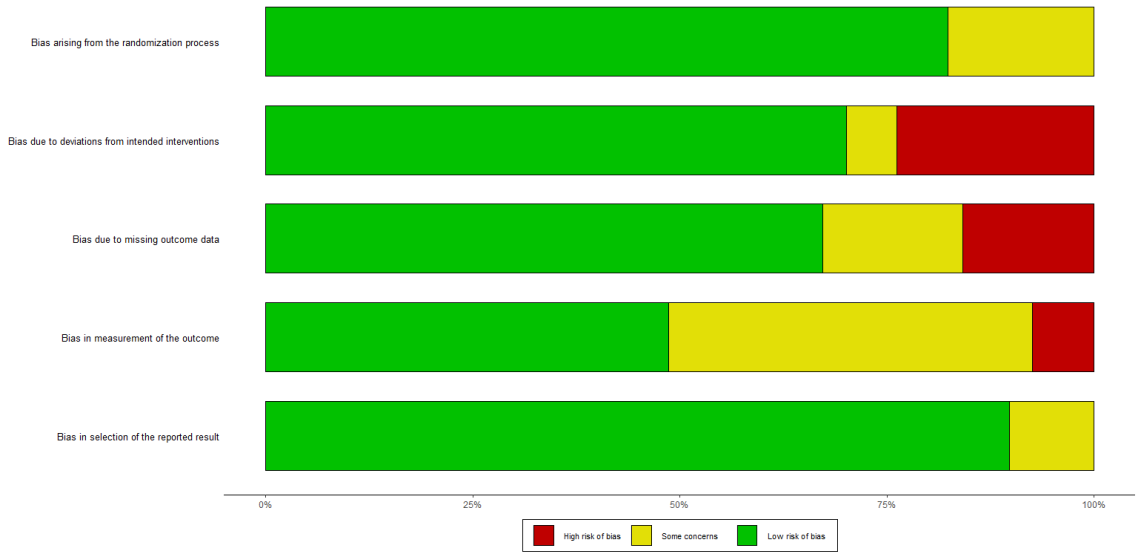

Figure 3. Distribution of the risk bias in the selected studies.

Table 2. Selected randomized-controlled trials on cell therapy for patellar and Achilles tendinopathy

	Clarke et al, 2010	de Vos et al, 2010	Vetrano et al, 2013	Kearney et al, 2013	Dragoo et al, 2014	Krogh et al, 2016	Boesen et al, 2017	Thermann et al, 2020
Title	Skin-Derived Tenocyte-like Cells for the Treatment of Patellar Tendinopathy.	Platelet-Rich Plasma Injection for Chronic Achilles Tendinopathy.	Platelet-Rich Plasma Versus Focused Shock Waves in the Treatment of Jumper's Knee in Athletes	Achilles's tendinopathy management: A pilot randomized controlled trial comparing platelet-rich plasma injection with an eccentric loading program	Platelet-Rich Plasma as a Treatment for Patellar Tendinopathy.	Ultrasound-Guided Injection Therapy of Achilles Tendinopathy with Platelet-Rich Plasma or Saline.	Effect of High-Volume Injection, Platelet Rich Plasma, and Sham Treatment in Chronic Midportion Achilles Tendinopathy	Endoscopic debridement for non-insertional Achilles's tendinopathy with and without platelet-rich plasma
Type of study	RCT	RCT	RCT	RCT	RCT	RCT	RCT	RCT
Sample size (Patients, n)	60	54	46	20	21	24	57	36
Age (years)	36, 20-51	49.5	18 to 50	35 to 66	35	49.2 ± 9.4	41.6	18 to 70
Main condition	PT	AT	PT	AT	PT	AT	AT	AT
Active group (injection)	Skin-derived tendon-like cells	L-PRP	P-PRP	L-PRP	Leukocyte rich PRP	L-PRP	P-PRP	P-PRP
Kit	None	GPS III Platelet Separation System (Biomet Biologics)	MyCells Autologous Platelet Preparation System	GenesisCS Component Concentration System (Emcyte)	GPS III Platelet Separation System (Biomet Biologics)	GPS II Platelet Separation System (Biomet Biologics)	Arthrex Double Syringe System	Arthrex Double Syringe System
Outcomes	VISA-P	VISA-A	VISA-P	VISA-A	VISA-P	VISA-A	VISA-A	VISA-A
Follow-up (weeks)	26	24	48	24	12	24	24	48
Score results (per protocol)	75 ± 17; 70 ± 14	68.4 ± 22.1; 73.1 ±22.5	91.3± 9.9; 77.6 ± 19.9	76 ± 23; 57 ± 27	67.8 ± 21.9; 83.9 ± 9	23 ± 2; 31.7 ± 13.7	19.6 ± 4.5; 8.8 ± 3.3	92.2± 8.2; 89.5 ±10.7

The controls interventions were divided into tendon injections using saline solution (Clarke, 2010; de Vos, 2010; Krogh, 2016; Boesen, 2017), dry needling (Dragoo, 2014), and endoscopic debridement (Thermann, 2020); and two studies used non-injections such as eccentric exercise (Kearney, 2013), and extracorporeal shock wave (Vetrano, 2013).

One author evaluated the skin-derived tenocyte-like cells to treat patellar tendinopathy (Clarke, 2010). This article demonstrated in the cell group an improvement in mean VISA scores from 44 ± 15 before treatment to 75 ± 17 at six months. In the placebo group (plasma), mean VISA scores before treatment were 50 ± 18, improving to 70 ± 14 at six months. They were estimated that the average difference in scores between groups was 8.1 (95% CI, 2.4 to 13.7; P = .006), with a significantly higher score in the cell therapy group.

Another publication demonstrated that the mean VISA-A score improved after 24 weeks in the PRP group by 21.7 points (95% CI, 13.0-30.5) and in the placebo group by 20.5 points (95% CI, 11.6-29.4) (de Vos, 2010). That is means the increase was not significantly different between both groups (adjusted between-group difference from baseline to 24 weeks, −0.9 (95% CI, −12.4 to 10.6).

Another author showed significantly better improvement than the control group (extracorporeal shock wake therapy, (ESWT)) at 12 months of follow-up (91.3 ± 9.9 vs. 77.6 6 ± 19.9; P =.026) in the VISA-P score. In other words, this article demonstrated that therapeutic injections of PRP lead to better midterm clinical results compared with focused ESWT in the treatment of jumper's knees in athletes (Vetrano, 2013).

An article showed that mean VISA-A in the intervention group (eccentric loading program plus PRP injection) was 76.0 (95% CI, 58.3 to 93.7) versus 57.4 (95% CI, 38.1 to 76.7) in the control group (an eccentric loading program plus a saline injection) for mid -substance Achilles tendinopathy at the six months of follow up was no statistically significant difference (Kearney, 2013).

Then, investigators showed that the intervention group (Leukocyte Rich Platelet Rich injection plus eccentric exercises program) improved significantly more than the control group (dry needling plus eccentric exercises program) at 12 weeks (P = .02). However, the difference was not maintained at 26 weeks (P = .66) of the study. Even at the end of this period, the VISA Score was superior in the control group (83.9 ± 9.0; 95% CI, 78.0 – 89.8) than the active group (67.8 ± 21.9; 95% CI, 53.4 – 82.1) (Dragoo, 2014).

In contrast, a study published in 2016 showed that VISA-A score at three months of follow up there was no statistically significant difference between the intervention group (PRP injection) and placebo group (saline injection). The groups were analyzed at the end of the follow-up (12 months), and the results were not statistically significant. The mean of the PRP group was 23.0 ± 2.0 and in the saline group was 31.7 ± 13.7. The authors also reported the mean difference with 95% CI between groups with -8.7 (-70.0 to 52.4), and the p-value was 0.740. (Krogh, 2016)

One year later, investigators compared PRP injection with high volume injection and placebo. In these three groups, all patients received detailed instruction on the standardized rehabilitation and eccentric program. At 24 weeks, VISA-A improvement was significantly (P < .01) in both the HVI (22.2 ± 4.6) and PRP (19.6 ± 4.5) groups compared with the placebo group (8.8 ± 3.3) (Boesen, 2017).

In our final article analyzed, compared two groups. The intervention group presented PRP injection, and the control group was endoscopic debridement only. The PRP showed a mean of 92.2 ± 8.2, and the placebo group 89.5 ± 10.7. The VISA-A score showed no significant between the groups at any point in time (P = 0.396) (Thermann, 2020).

Outcome of meta-analysis

The eight studies have reported VISA scores as a functional outcome. Significant heterogeneity was reported (Q=43.92, df=7, p=0.01, I2=84%), suggesting 84% of the variability in treatment effect estimates is due to fundamental study differences (heterogeneity) and only 16% due to chance. This is evident from the wide scatter of effect estimates with little overlap in their confidence intervals, as demonstrated in **Figure 4.** The random-effects model overall result was no significant (SMD=0.43, 95% CI (-0.52, 1.38), t=1.07, p=0.32), and the confidence interval does contain zero, there is strong evidence that, on average, the treatment effect is not beneficial in this outcome.

In the subgroup analysis, four studies (de Vos, 2010; Kearney, 2013; Dragoo, 2014; Krogh, 2016) have reported LR-PRP. Three studies (Vetrano, 2013; Boesen, 2017; Therman, 2020) have reported LP-PRP. Only one study (Clarke, 2010), used skin-derived tendon-like cells. There was no significant difference between groups (Q=3.49, df=2, p=0.17) in the random-effect model.

Study name	Statistics for each study							Sample size		Weight (Fixed)		Residual (Fixed)		
	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Treated	Control	Relative weight	Relative weight	Std Residual	Std Residual	Std Residual
Clarke et al (2010)	0.314	0.258	0.066	-0.191	0.819	1.218	0.223	33	27	23.04		-0.38		
De Vos et al (2010)	-0.208	0.269	0.072	-0.735	0.319	-0.772	0.440	27	27	21.16		-2.54		
Vetrano et al (2013)	0.857	0.303	0.092	0.262	1.451	2.825	0.005	23	23	16.64		1.65		
Kearney et al (2013)	0.726	0.443	0.197	-0.144	1.595	1.636	0.102	10	10	7.78		0.77		
Dragoo et al (2014)	-0.935	0.488	0.238	-1.892	0.022	-1.915	0.055	8	9	6.42		-2.82		
Krogh et al (2016)	-0.604	0.726	0.527	-2.026	0.819	-0.832	0.406	2	6	2.90		-1.40		
Boesen et al (2017)	2.680	0.442	0.195	1.813	3.546	6.062	0.000	19	19	7.83		5.37		
Thermann et al (2020)	0.275	0.328	0.108	-0.368	0.918	0.838	0.402	17	19	14.22		-0.41		
	0.399	0.124	0.015	0.156	0.641	3.224	0.001							

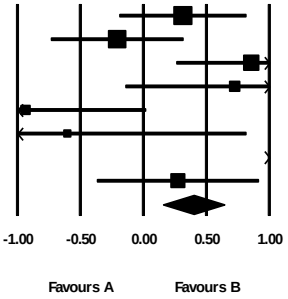

Figure 4. Forest plot of the comparison between the experimental and placebo groups.

As for injection site was analyzed, five studies (de Vos, 2010; Kearney, 2013; Krogh, 2016; Boesen, 2017;
Thermann, 2020) have reported injection in the AT site. Three studies (Clarke, 2010; Vetrano, 2013; Dragoo, 2014), have reported injection in the PT site. There was no significant difference between groups (Q=0.36, df=1, p=0.55) in the random-effect model.

Figure 5 shows the funnel plot of this article. The vertical line shows the average effect size because we used a random-effects model. The studies' distribution is asymmetrical because some studies (de Vos, 2010; Dragoo, 2014; Boesen, 2017) do not seem to follow the funnel pattern well either.

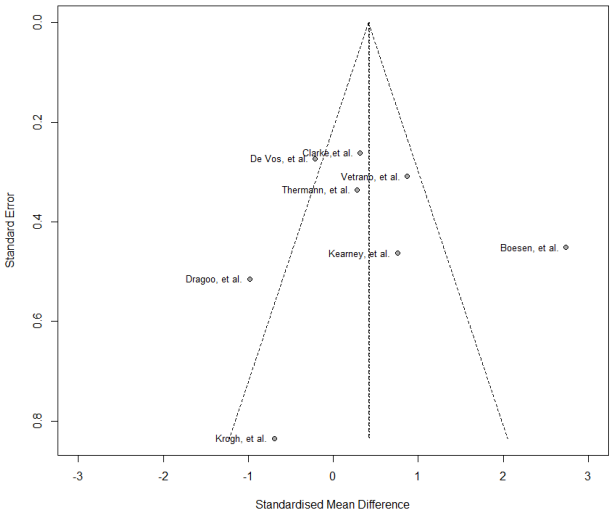

Figure 5. Funnel plot

Overall, the data set shows an asymmetrical pattern in the funnel plot that might indicate publication bias. However, in **Figure 6,** a contour-enhanced funnel plot was performed to demonstrate how asymmetry patterns relate to statistical significance. The plot includes three different colors regions which signify the significance level of each study. There is no evidence to conclude a publication bias.

Egger's regression test results (β^0=0.37, 95% CI (-5.7, 6.45), t=0.12, p=0.91) indicate that the intercept of the regression model is not significantly larger than zero and indicates that the data in the funnel plot is not asymmetrical.

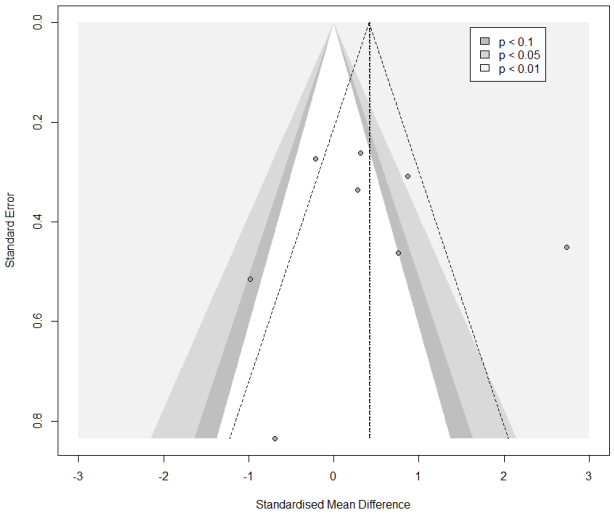

Figure 6. Contour-enhanced funnel plot

DISCUSSION

This article compared regenerative therapy injections to other therapeutical modalities in patients with Achilles and patellar tendinopathies. The primary outcome was measured as a change in function of patients using VISA score (VISA-A and VISA-P). All eight studies evaluated the VISA. Three studies used the VISA-P, and the rest of the studies applied the VISA-A) scores – which is a strong advantage compared to other meta-

analysis reports and systematic reviews – in similar cut point periods.

The performed analysis using a random-effects model overall showed no significant difference between the experimental and control groups (SMD=0.43, 95% CI (-0.52, 1.38), t=1.07, p=0.32), and significant heterogeneity was reported (Q=43.92, df=7, p=0.01, I2=84%). Therefore, the treatment effect is not beneficial in the functional outcome measured with this clinical instrument.

At the end of the database and metasearch process, eight articles were included in the meta-analysis. However, there were some limitations in these studies that might impact the final results. Firstly, articles were published with ten years of differences since their publication, impacting the technology of regenerative therapy. Also, the kit´s preparation was different between these studies. Moreover, the applications of intervention depend on the professional-level training and experience who apply regenerative therapy. Another factor that could impact the validity of the results is the number of participants and the age dispersion of the participants.

Apparently, ultrasound-guided injection of autologous skin-derived tendon-like cells can be safely used to treat PT with, in the short term, the faster response of treatment and significantly greater improvement in pain and function than an injection of plasma alone. However, no further results have been published to date using the interventions reported by (Clarke, 2010).

In one article differences in favor of treatment were demonstrated at week 6. But there were no differences at weeks 12 and 24 (de Vos, 2010). This may be due to the lack of standardization of the exercise training plan. Furthermore, the authors point out that a limitation of their studies is that the number of platelets and the number of activated growth factors present in the PRP injections were unknown.

Also, results published showed better results in the late phases of follow-up. That is, in the 6 and 12 months after the intervention (Vetrano, 2013). These authors were the only ones to use ESWT. The authors hypothesize that their results could be explained because the pathway of chronic tendinopathies is very complex and involves, in addition to growth factors, many other pathogenetic factors that operate at different stages of the disease. Furthermore, the exact action mechanisms of ESWT and PRP are not yet fully understood.

Investigators demonstrated no statistically significant difference between the two treatments in a pilot study (Kearney, 2013). However, this may be secondary to a type II error due to the small sample size in each group analysis. This article shows that the methodology is feasible, and more investigations will be necessary to probe the therapy's effectiveness.

One paper demonstrated that the intervention group accelerates the recovery from PT relative to exercise and ultrasound-guided dry needling alone (Dragoo, 2014). The apparent benefit of PRP dissipates over time. According to the authors, this situation could be explained by the effect that a single PRP injection may wear off over time. Another explanation could be that the high leukocyte content of the PRP presented an initial inflammatory response but not at the end of the process.

Another article reported that no differences between the groups at three months of evaluation in the VISA-A score (Krogh, 2016). They were not obtained at the end of the follow-up either. This situation could be explained because, at 12 months of follow-up, only 8 of 24 patients were left in the study, 2 in the PRP group and 6 in the saline group, losing analysis consistency. According to the authors, many patients withdrew from the trial because the therapies used did not provide the anticipated pain relief that the participants had expected.

An article published confirms the positive clinical effect in the functional questionary using an eccentric program with a combination with multiple PRP injections compared with exercise training alone at the end of follow-up (Boesen, 2017).

In contrast, another publication demonstrated that the addition of PRP injection did not improve the final score in the VISA questionary compared to the debridement technique alone (Thermann, 2020).

The groups that used Leukocyte Rich Platelet Rich had different results vs. the groups that used Leukocyte Poor Platelet Rich Plasma. Moreover, both groups were compared separately, but the results were not categorical. In general, the available literature has already demonstrated seemingly positive results of such interventions in this population. However, the most common outcome measure is pain, and the diagnostic method is not standardized.

This meta-analysis enabled us to show a more robust measure of the efficacy of regenerative therapy in this setting by limiting the selection criteria, the underlying condition, and the treatment approach to patellar and Achilles tendinopathy. In this meta-

analysis, most of the results were reported at the end of the study period, approximately at week 24. However, most of the positive results seemed to be found in shorter periods, mainly between weeks 4 and 6. Hence, these findings suggest that perhaps cell therapy for patellar and Achilles tendinopathy could be effective in the short and medium terms but not in the long run.

LIMITATIONS

Several methodological issues among the available articles were found in the literature. Therefore, it would be imperative for future studies to standardize both the diagnostic approach and the assessment of outcomes in this scenario to better report study results with standardized measures.

The individual effect of each treatment modality should be evaluated as a global effect of both regenerative therapy and physical exercise since, in most studies, patients followed a somewhat vaster training plan.

The heterogeneity of the presented results may be explained by the differences between SC and PRP (LR-PRP, LP-PRP) products, including those between the doses used in each study and other variables not considered in this meta-analysis. Different types of tendinopathy may also be explained (i.e., partial tendon tear versus tendinitis or tendinosis alone without a tear) could benefit differently from this kind of treatment, but in these articles, those differences in diagnosis were not included at the moment of recruitment.

Finally, I2 should be interpreted cautiously when a meta-analysis has few studies because the heterogeneity statistic I2 can be biased in small meta-analyses (von Hippel, 2015).

CONCLUSION

This article analyzed the efficacy of regenerative therapy (SC and PRP) in functional outcomes in the treatment of PT and AT. This meta-analysis does not provide enough evidence to support regenerative therapy for the management of patellar and Achilles tendinopathies. Several limitations of the studies included unequal samples sizes, different imaging classifications - the size of tendon tear or hypoechogenicity magnitude- patient follow-up, and even different risks of bias score. Other variables, such as dosage (intensity, duration, and frequency of injections), autologous blood quality, platelet concentration, comorbidities, and complementary therapies such as exercise training in managing these tendinopathies, should be considered in future studies. This new evidence is not a definitive conclusion. Further research is necessary to provide more robust evidence to establish the effectiveness of cell therapies for AT and PT.

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Conflict of interest

There are no personal or financial conflicts of interest to declare. All listed authors have completed the International Committee or Journal of Medical Journals Editors (ICMJE) form to address potential conflicts of interest. All authors approved the final version of this manuscript.

REFERENCES

Bass, E. (2012). Tendinopathy: why the difference between tendinitis and tendinosis matters. Int J Ther Massage Bodywork. 5(1):14–17.

Boesen, A. Hansen, R. Boesen, M. Malliaras, P. Langberg, H. (2017). Effect of High-Volume Injection, Platelet-Rich Plasma, and Sham Treatment in Chronic Midportion Achilles Tendinopathy: A Randomized Double-Blinded Prospective Study. The American Journal of Sports Medicine. 45(9), 2034–2043.

Clarke, A. Alyas, F. Morris, T. Robertson, C. Bell, J. Connell, D. (2010). Skin-Derived Tenocyte-like Cells for the Treatment of Patellar Tendinopathy. The American Journal of Sports Medicine. 39(3), 614–623.

Costa-Almeida, R. Calejo, I. Gomes, M. (2019) Mesenchymal Stem Cells Empowering Tendon Regenerative Therapies. Int J Mol Sci. 20(12):3002.

De Vos, R. Weir, A. Van, H. Bierma-Zeinstra, S., Verhaar, J. Weinans, H. Tol, J. (2010). Platelet-Rich Plasma Injection for Chronic Achilles Tendinopathy. JAMA. 303(2), 144.

Dragoo, J. Wasterlain, A. Braun, H. Nead, K. (2014). Platelet-Rich Plasma as a Treatment for Patellar Tendinopathy. The American Journal of Sports Medicine. 42(3), 610–618.

Greenhalgh, A. Jonathan S. (2014). Comparison of achilles tendon loading between male and female recreational runners. Journal of Human Kinetics volume 44, 155-159.

Hedges, G. (2018). Statistical Engineering Division. National Institute of Standards and Technology (NIST). Vol 2.

Higgins, J. Savović, J. Page, M. Elbers, R., Sterne, J (2021). Chapter 8: Assessing risk of bias in a randomized trial.). Cochrane Handbook for Systematic Reviews of Interventions version 6.2

Ho, J. Sawadkar, P. Mudera, V. (2014). A review on the use of cell therapy in the treatment of tendon disease and injuries. Journal of Tissue Engineering. Volume 5: 1 –18

Hopkins, C. Fu, S. Chua, E. Hu, X. Rolf, C. Mattila, V. Qin, L. Shu-hang, P. Chan, K. (2016). Critical review on the socio-economic impact of tendinopathy. Asia Pac J Sports Med Arthrosc Rehabil Technol. 4:9–20.

Korakakis, V. Kotsifaki, A. Stefanakis, M. Sotiralis, Y. Whiteley, R. Thorborg, K. (2021). Evaluating lower limb tendinopathy with Victorian Institute of Sport Assessment (VISA) questionnaires: a systematic review shows

very-low-quality evidence for their content and structural validity—part I. Knee Surg Sports Traumatol Arthroscopy. 29:2749–2764.

Krogh, T. Ellingsen, T. Christensen, R. Jensen, P. Fredberg, U. (2016). Ultrasound-Guided Injection Therapy of Achilles Tendinopathy With Platelet-Rich Plasma or Saline. The American Journal of Sports Medicine. 44(8), 1990–1997.

Li, H. Hua, Y. (2016). Achilles Tendinopathy: Current Concepts about the Basic Science and Clinical Treatments. Biomed Res Int. Volume 2016:6492597.

Liu, L. Hindieh, J. Leong, D. Sun, H.(2017) Advances of stem cell based-therapeutic approaches for tendon repair. J Orthop Translat. Volume 9: 69–75.

Lui, P. (2015). Stem cell technology for tendon regeneration: current status, challenges, and future research directions. Stem Cells Cloning: Advances and Applications. 8:163–174.

Madhi, I. (2020). The use of PRP in treatment of Achilles Tendinopathy: A systematic review of literature. Study design: Systematic review of literature. Annals of Medicine and Surgery. 55:320-326.

Mathur, M. VanderWeele, T. (2020). Sensitivity analysis for publication bias in meta-analyses. Journal of the Royal Statistical Society. Series C, Applied statistics, 69(5), 1091–1119.

Maffulli N, Wong J, Almekinders LC. (2003). Types and epidemiology of tendinopathy. Clin Sports Med, 22(4):675–692.

Mead, M. Gumucio, J. Awan, T. Mendias, C. Sugg, K. (2018). Pathogenesis and Management of Tendinopathies in Sports Medicine. Transl Sports Med. 1(1):5–13.

Miller, L. Parrish, W. Roides, B. Bhattacharyya, S. (2017) Efficacy of platelet-rich plasma injections for symptomatic tendinopathy: systematic review and meta-analysis of randomised injection-controlled trials. BMJ Open Sport Exerc Med. 3(1).

Ntege, E. H., Sunami, H., & Shimizu, Y. (2020). Advances in regenerative therapy: A review of the literature and future directions. Regenerative therapy, 14, 136–153.

Page, M. McKenzie, J. Bossuyt, P. Boutron, I. Hoffmann, T. Mulrow, C. (2020). PRISMA. Statement: an updated guideline for reporting systematic reviews. BMJ.

Ramaswamy, S. Reddy, R. Babu, N. Ashok, G. (2018). Stem-cell therapy and platelet-rich plasma in regenerative medicines: A review on pros and cons of the technologies. J Oral Maxillofac Pathol. 22(3):367-374.

Riley, R. Higgins, J. Deeks ,J. (2011). Interpretation of random effects meta-analyses BMJ, 342:d549.

Robinson, J. Cook, J. Purdam, C. Visentini, P. Ross, J. Maffulli, N. Taunton, J. Khan, K. (2001). The VISA-A questionnaire: a valid and reliable index of the clinical severity of Achilles tendinopathy. British Journal of Sports Medicine. 35:335-341.

Ruzzini, L. Longo, U. Rizzello, G. Denaro, V. (2012) Stem cells and tendinopathy: state of the art from the basic science to clinic application. Muscles Ligaments Tendons Journal. 2(3):235–238.

Schwartz, A. Watson, J. Hutchinson, M. (2015). Patellar Tendinopathy. Sports Health. 7(5):415–420.

Simpson, M. Rio, E. Cook, J. (2016) At what age do children and adolescents develop lower limb tendon pathology or tendinopathy? A systematic review and meta-analysis. Sport Med. 46(4):545–57.

Smith, R. (2013). cell therapy for tendinopathy: lessons from a large animal model. British Journal of Sports Medicine 47:e2.

Sullivan, G. Feinn, R. (2012). Using Effect Size-or Why the P Value Is Not Enough. J Grad Med Educ. 4(3):279-282.

Tan, S. Chan, O. (2008). Achilles and patellar tendinopathy: current understanding of pathophysiology and management. Disabil Rehabil. 30(20-22):1608-15.

Van den Boom, N. Winters, M. Haisma, H. Moen, M. (2020). Efficacy of Stem Cell Therapy for Tendon Disorders: A Systematic Review. Orthop J Sports Med. 8(4):2325967120915857.

Vicenzino, B. de Vos, R. Alfredson, H. Bahr, R. Cook, J. Coombes, B. Fu, S. Gravare, K. Grimaldi, A. Lewis, J. Maffulli, N. Magnusson, S. Malliaras, P. Auliffe, S. Oei, E. Purdam, C. Rees, Rio, E. Scott, A. Speed, C Akker-Scheek, I. Weir, A. Moriatis, J. Zwerver, J. (2020). ICON 2019-International Scientific Tendinopathy Symposium Consensus: there are nine core health-related domains for tendinopathy (CORE DOMAINS): Delphi study of healthcare professionals and patients. Br J Sports Med. 54:444–451.

Visentini, P. Khan, K. Cook, J. Kiss, Z. Harcourt, P. Wark, J. (1998). The VISA score: an index of severity of symptoms in patients with jumper's knee (patellar tendinosis). Victorian Institute of Sport Tendon Study Group. J Sci Med Sport. 1(1):22-8.

Von-Hippel, P. (2015). The heterogeneity statistic I2 can be biased in small meta analyses. BMC Med Res Methodol. 15, 35.

Wang, Y. Han, C. Hao, J. Ren, Y. Wang, J. (2019). Efficacy of platelet-rich plasma injections for treating Achilles tendonitis : Systematic review of high-quality randomized controlled trials. Orthopade. 48(9):784-791.

Xu, Y., & Murrell, G. A. (2008). The basic science of tendinopathy. Clinical orthopaedics and related research, 466(7), 1528–1538.