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1 **Title: Cell-based therapies for the treatment of sports injuries of the upper limb**

2  
3 Running heading: Cell-based therapies for upper limb sports injuries

4  
5 Authors:

6 Kwaku Baryeh MBBS MRCS(Ed), Research Fellow, Academic Surgical Unit, South West London Elective  
7 Orthopaedic Centre, Epsom, United Kingdom

8  
9 Vipin Asopa PhD, FRCS (Tr & Orth), MBChB, Consultant Orthopaedic Surgeon, Academic Surgical Unit, South  
10 West London Elective Orthopaedic Centre, Epsom, United Kingdom

11  
12 Nardeen Kader MBChB MRCS, Research Fellow, Academic Surgical Unit, South West London Elective  
13 Orthopaedic Centre, Epsom, United Kingdom

14  
15 Nick Caplan PhD PgCert BSc (Hons) FHEA, Head of Sport, Exercise and Rehabilitation department and  
16 Professor of Aerospace Medicine & Rehabilitation, Faculty of Health and Life Sciences, Northumbria University,  
17 Newcastle upon Tyne, United Kingdom

18  
19 Nicola Maffulli MD MS PhD FRCP FRCS (Orth), Consultant Orthopaedic Surgeon and Honorary Professor for  
20 Sports and Exercise Medicine, Centre for Sports and Exercise Medicine, Barts and The London School of  
21 Medicine and Dentistry, Mile End Hospital, Queen Mary University of London, London, England.  
22 Department of Musculoskeletal Disorders, Faculty of Medicine and Surgery, University of Salerno, Salerno, Italy.  
23 Department of Medicine, Surgery and Dentistry, University of Salerno, Via S. Allende, Baronissi (SA), Italy.  
24 School of Pharmacy and Bioengineering, Keele University Faculty Of Medicine, Stoke on Trent, United Kingdom

25  
26 Deary Kader MBChB, FRCS, FRCSEd, FRCSGlas, FRCS (Tr & Orth) MFSEM (UK), Consultant Orthopaedic  
27 and Trauma Surgeon, Academic Surgical Unit, South West London Elective Orthopaedic Centre, Epsom, United  
28 Kingdom and visiting Professor Faculty of Health and Life Sciences, Northumbria University, Newcastle upon  
29 Tyne, United Kingdom.

30  
31  
32  
33 Corresponding author: Nicola Maffulli  
34 Email address: [n.maffulli@qmul.ac.uk](mailto:n.maffulli@qmul.ac.uk)

36 **Abstract**

37 **Introduction**

38 The use of cell-based therapies in the management of sports injuries of the upper limb is increasingly popular  
39 despite the limited scientific evidence available for their use. We aim to evaluate the evidence for the use of cell-  
40 based therapies in these injuries and recommend areas for further research.

41

42 **Areas Covered**

43 In accordance with a published protocol (PROSPERO; Registration No. CRD42020193258), a comprehensive  
44 search of the literature was performed using the MEDLINE and EMBASE databases from inception to June 2020.  
45 All human studies reporting on the clinical, histological or radiological outcomes following the use of cell-based  
46 therapies in the management of epicondylitis or rotator cuff pathology were included in this study. This resulted in  
47 22 studies being included in this review, all of which underwent risk of bias assessments.

48

49 **Expert opinion**

50 The evidence for the use of cell-based therapies in upper limb sports injuries is limited and generally of low  
51 quality. Given the heterogeneity in the cell types used, their harvesting methods and cell amounts, future research  
52 should be targeted at developing standardisation of the reporting of these studies and more direct comparative  
53 studies looking at the efficacy of the different cell types.

54

55 **Keywords:** cell-based therapies; epicondylitis; MSC; rotator cuff pathology; sports injuries; tenocytes

56

57 **Highlights**

- 58
- Of the 22 studies included (16 rotator cuff pathology and 6 epicondylitis) 3 were level 1 evidence, 3 were  
59 level 2 evidence with the remaining 16 being level 3 or below
  - In the non-randomised studies, the magnitude of effect of intervention on clinical scores was mostly  
60 large. In the randomised controlled trials, the effect magnitude of cell-based therapies was only small to  
61 medium
  - Within the limitations of the included studies, tenocytes showed the most promising results for the  
62 treatment of epicondylitis, whilst bone marrow concentrate demonstrated the most promising results for  
63 the treatment of rotator cuff pathology
  - The rate of complications in the included studies was low, with none of the complications reported being  
64 directly attributable to the use of cell-based therapies
  - Future research should focus on standardisation of cell-based therapies to allow for the reproducibility of  
65 treatments that are shown to be effective
- 66
- 67
- 68
- 69

70

71 **1. Introduction**

72 Injuries of the upper limb are debilitating to athletes, with tendinopathies of the shoulder and elbow being  
73 amongst the most prevalent [1]. Rotator cuff pathology represents the most common shoulder pathology for which  
74 patients seek medical attention [2], and epicondylitis represents a prevalent cause of patients presenting with  
75 elbow pain [3]. Despite the prevalence of these conditions, the success of the currently available treatment options  
76 is variable, with the rate of re-tear following rotator cuff repair reported to range from 20% to as high as 94%  
77 [4,5], and recurrence rates of up to 25% in non-operatively treated epicondylitis [6].

78 One of the reasons for the difficulty in treating these injuries is the complex organisation of the area of insertion  
79 of tendons into the bone, the enthesis. The enthesis is comprised of four zones: tendon, unmineralized  
80 fibrocartilage, mineralized fibrocartilage, and bone [7]. Rotator cuff and epicondylar tendinopathy share common  
81 histological features [8]. Often, following surgical repair, fibrovascular scar tissue forms between tendon and bone  
82 resulting in a weakened construct, and subsequent failure of repair [9]. This inability to restore the normal biology  
83 of the tendon has meant that, despite technical advances in surgical treatment, failure rates are still high. However,  
84 cell-based therapies have shown promise in their ability to restore the natural biology of damaged tendons [10].  
85 Cell-based therapies include a multitude of treatment modalities using cells at various stages of differentiation.  
86 Given their potential applications in musculoskeletal medicine [11,12], it is not surprising that their popularity  
87 continues to increase [13]. At the heart of these advancements are mesenchymal stem cells (MSC) and  
88 tenocytes[14,15].

89 Mesenchymal stem cells are multipotent cells able to differentiate into any type of cell of mesodermal lineage *in*  
90 *vitro*; these include chondrocytes, osteocytes and adipocytes[16]. However, *in vivo*, this has not yet been  
91 demonstrated [17–19]. Tenocytes also have some limited potential as a progenitor cell[20]. These unique abilities  
92 render cell-based preparations a potentially invaluable tool in the treatment of musculoskeletal sports injuries, and  
93 may offer a quicker return to sport[21–23]. *In vivo*, the therapeutic effect of MSC are likely resulting from their  
94 trophic, paracrine and immunomodulatory functions as opposed to proliferation and differentiation [24–26]. Much  
95 like MSC, tenocytes stimulate growth factors and other immunomodulatory cells to promote a healing response  
96 [27].

97 The term MSC was coined by Caplan in 1991 [28]. Despite their name, MSC are not stem cells. The National  
98 Institutes of Health (NIH) defined stem cell as a cell from the embryo, fetus, or adult that has, under certain  
99 conditions, the ability to reproduce itself for long periods (long-term self-renewal), remain unspecialized or  
100 differentiate to specialised cells[29]. Neither MSC or tenocytes have this ability, and so cannot be called stem

101 cells. As a result, the International Society for Cellular referred to these cells as mesenchymal *stromal* cells[30].  
102 Indeed, Caplan himself advocated a change in nomenclature from MSC to ‘medicinal signalling cells’ to better  
103 reflect their *in vivo* secretory function [31]. However, the term MSC has persisted, and there are currently several  
104 clinicians overstating the capabilities of these cell-based therapies, with a rapid rise in the number of rogue ‘stem  
105 cell’ clinics [32].

106 The most common sources of MSC are bone marrow and adipose tissue[33,34]. They are found infrequently in  
107 bone marrow, making up less than 0.01% of mono-nucleated cells[16,35,36] or a few hundred cells per  
108 millilitre[37]. In contrast, adipose tissue contains roughly 400,000 MSC per millilitre of lipoaspirate[38]. To  
109 increase the concentration of these cells further, processing is performed; the concentrate produced is, thus,  
110 referred to as bone marrow concentrate (BMC) for bone marrow or the stromal vascular fraction (SVF) in the case  
111 of lipoaspirate[39,40]. Given the heterogeneity of the sources of MSC, one could be forgiven for failing to see the  
112 common link. Recent studies have identified the pericyte as the origin of most, if not all, MSC [41]. Pericytes are  
113 ubiquitous and found in all vascularized tissues, as such, MSC can be isolated from all vascularized tissues [25].  
114 This means that, in the event of vessel damage, the released pericytes, activated by the injury, become MSC  
115 engendering a regenerative environment to promote healing of the injured tissue [17].

116 Cell-based therapies for the treatment of sports related injuries are being increasingly used given the relative  
117 safety of their use, quicker return to sport and ability to treat tissues that are slow or difficult to heal [42]. Despite  
118 their clear potential, cell-based therapies have little scientific evidence for their use. This review aims to address  
119 two central questions: what the available evidence for the use of cell-based therapies in the treatment of rotator  
120 cuff and epicondylar injuries is, and where should future research be directed.

121

122 **2. Methods**

123 **2.1 Search strategy**

124 This study was performed in line with the Preferred Reporting Items for Systematic Review and Meta-Analysis  
125 (PRISMA) guidelines[43]. It was prospectively registered on the International prospective register of systematic  
126 reviews (PROSPERO; Registration No. CRD42020193258).

127

128 A preliminary search of the literature on regenerative cell use in common sports injuries was performed. Several  
129 articles were found encompassing both lower limb and upper limb injuries. A separate review investigating the  
130 pathologies associated with lower limb injuries was performed [44]. Given the difficulties associated with  
131 enthesopathies, a decision was made to focus on the two most common and difficult to treat upper limb  
132 enthesopathies, namely rotator cuff and epicondylar injuries.

133

134 A sensitive search strategy for multiple databases was devised by one author (NK). A comprehensive search of  
135 the literature was performed using the MEDLINE and EMBASE databases from inception to June 2020. Article  
136 titles were searched for the following terms, limited to humans, as well as their corresponding or related MeSH  
137 terms: ‘mesenchymal stem cell’ OR ‘stem cell’ OR ‘stromal vascular fraction’ OR ‘bone marrow’ OR ‘tenocyte’  
138 in two separate searches where they were combined with the following:

139 Search 1, MSC use in rotator cuff pathology, all fields limited to ‘Human’:

140 AND ‘rotator cuff’ [KEYWORD] OR ‘rotator cuff injury’ [KEYWORD] OR related MeSH terms.

141

142 Search 2, MSC use in epicondylar tendinopathy, all fields limited to ‘Human’:

143 AND ‘epicondylitis’ [KEYWORD] OR ‘tennis elbow’ [KEYWORD] OR related MeSH terms.

144

145 To search the grey literature, each trial registry was searched for ‘mesenchymal stem cell’ and ‘regenerative cell’  
146 on 06.06.2020 using the following databases to capture any results from finished trials with unpublished results:

147 CENTRAL trials registry of the Cochrane Collaboration, WHO International Clinical Trials Registry Platform  
148 (ICTRP), EU Clinical Trials Register and ClinicalTrials.gov.

149 The references of included studies were also searched manually for further relevant studies.

150

151

152 **2.2 Eligibility criteria**

153 Studies were included if the following inclusion criteria (PICOS) were met:

154 Population. Male and female humans who have either epicondylitis or rotator cuff pathology.

155

156 Interventions. The use of cell-based therapies including mesenchymal stem cells, tenocytes, tenocyte-like cells  
157 and any processed or concentrated cell preparations thought to contain mesenchymal stem cells such as stromal  
158 vascular fraction, bone marrow concentrate.

159

160 Control. Patients with epicondylitis or rotator cuff pathology treated without the use of cell-based therapies.

161

162 Outcomes. Studies had to contain clinical outcomes such as patient reported outcome measures (PROMs),  
163 histological analysis of tendon tissue pre- and post-intervention or imaging outcomes such as an evaluation of tear  
164 size or tendon healing following the use of cell-based therapies.

165

166 Study designs. Randomised controlled trials (RCT), controlled clinical trials (CT), retrospective studies, non-  
167 randomised studies, cohort studies, case series and case reports.

168

169 **2.3 Data collection**

170 Titles and abstracts were screened by two authors (NK and KB) for relevance. Following this, selection criteria  
171 were applied independently by two authors (NK and KB). If unclear from the review of the title and abstract  
172 whether a study was appropriate for inclusion, full texts were examined. Consensus was used to resolve any  
173 disagreements between reviewers, referring to a third, senior reviewer (VA) if consensus was not reached.

174

175 **2.4 Data extraction**

176 The following data were extracted: patient demographics (age, sex), nature of injury, intervention performed,  
177 biologic used and the source, cell count of biologic, functional outcomes (PROMs), radiological outcomes and  
178 length of follow up.

179

180 For all studies containing data presented as means with standard deviations or standard errors, values of all  
181 relevant outcome measures for pre and post-intervention were extracted in order to calculate the effect sizes.



182 **2.5 Quality assessment of included studies**

183 A risk of bias assessment was completed using the Cochrane Risk of Bias 2 (RoB2) tool for RCTs. This tool  
184 provides an algorithm by which an overall risk of bias judgment is reached per each study. Five domains were  
185 evaluated for risk of bias (the randomization procedure, deviations from the intended interventions, missing  
186 outcome data, measurement of the outcome, and selection of the reported result) by 2 authors (KB and NK)  
187 independently. Each domain was labelled as either high risk of bias, low risk of bias or some concerns. If a study  
188 had all five domains as low risk, the overall risk of bias would be low. However, if any of the five domains were  
189 labelled high risk or some concern, their overall risk of bias would also be high risk or some concern respectively.  
190 Any disagreements that arose were resolved by a third author (VA).

191

192 Case series, case control studies and cohort studies were assessed using the Agency for healthcare research and  
193 quality(AHRQ) tool[45]. Using this tool cohort, studies had a maximum of 13 stars, case-control studies had a  
194 maximum of 11 stars. and case series had a maximum of 9 stars, where the greater the number of stars the lower  
195 the risk of bias.

196

197 **2.6 Data analysis**

198 To provide an overall summary of the data extracted, for all studies containing data presented as means with  
199 standard deviations or standard errors, effect sizes were calculated for available outcomes. For RCTs, the mean  
200 difference between pre- and post-surgery were calculated for each outcome in both the intervention and control  
201 groups. Effect sizes were then calculated between the mean differences in the intervention and control group. For  
202 non-RCTs, effect sizes were calculated from the pre- and post-intervention data. Given the typically small sample  
203 size in each study, effect sizes were bias corrected using the Hedge's G method[46]. All calculated effect sizes  
204 were defined as small (0.2), medium (0.5), large (0.8) or very large (1.3) [47], and were presented in effect size  
205 plots with 95% confidence interval error bars.

206

207 Outcomes were grouped according to the injury they reflect: RC or epicondylitis. Injury patterns were further  
208 divided into RCT and non-RCT studies. Given the heterogeneity of the study protocols, a full meta-analysis was  
209 not possible.

210

211 **3. Results**

212 The primary search yielded 337 results (see PRISMA flowchart – Figure 1).

213 After reviewing full texts, both authors (NK, KB) agreed that 16 studies were eligible for inclusion. After

214 searching through the references of eligible studies and all relevant review articles manually, five further cited

215 studies were found to be eligible for inclusion. One additional study with available data was found by searching

216 the grey literature.

217 Of the 22 studies that met the inclusion criteria, 16 were relating to rotator cuff pathology and 6 to epicondylitis.

218 A summary of the main study characteristics can be found in Table 1.

219

220 **3.1 Risk of bias assessment**

221 The three included RCTs were assessed for risk of bias using the Cochrane RoB2 tool with all three displaying

222 some concerns for bias (see Table 2 and Figure 2[48]). 16 studies were assessed using the AHRQ tool (see

223 Table 3). The seven case series [49–55] had risk of bias assessment between 4 and 6 out of nine stars. The two

224 case control studies [56,57] had risk of bias assessments between 6 and 9 out of 11 stars. The seven cohort

225 studies [58–64] had risk of bias assessments between 6 and 10 out of 13 stars. The three case reports

226 [27,65,66] were assumed to be at a high risk of bias, and thus not assessed further.

227

228 **3.2 Shoulder: Rotator Cuff Injury**

229 Sixteen studies involving the use of cell-based therapies in rotator cuff disease were found. Seven studies assessed

230 augmentation of RC repair surgery, and nine evaluated the use of intra-articular, or intra-tendinous, injections.

231

232 **3.2.1 Bone Marrow Concentrate**

233 Three studies investigated the use of BMC alone. Two studies [55,56] involved BMC augmented surgical repair

234 of the RC and demonstrated maintained tendon integrity on MRI in 87% of patients at 10 years [56]and 100% of

235 patients at 12 months [55]. The remaining study [62] demonstrated improved pain and function scores following

236 BMC injection.

237

238 Ellera Gomes et al[55]reported on 14 patients with complete RC tears. All patients underwent an augmented mini-

239 open RC repair by a single surgeon and BMC was injected into the tendon and the bony footprint. This was

240 followed by 4 weeks immobilisation in a sling and physiotherapy thereafter. The UCLA shoulder score improved

241 from  $12 \pm 3$  pre-operatively to  $31 \pm 3.2$  at a minimum of 12 months follow up. Magnetic resonance imaging  
242 follow up was available in all patients at 12 months and all 14 patients demonstrated tendon integrity.

243

244 Hernigou et al[56]reported on 45 patients with supraspinatus tears matched for tear size and location, shoulder  
245 dominance, sex, and age with an equivalent group. All procedures were undertaken using arthroscopic techniques.  
246 In the experimental group, BMC were injected at the tendon bone junction and the bony footprint. In both groups,  
247 the first week post-operatively involved an arm sling and passive forward flexion. Active range of motion  
248 exercises were commenced at six weeks, and active resistance exercises at eight weeks. Light daily activities were  
249 allowed from two months, and heavy manual work or sporting activities allowed after six months. At the 10-year  
250 follow up MRI, 39 of 45 patients (87%) in the experimental group had intact RC compared to 20 of 45 patients  
251 (44%) in the control group ( $p < 0.05$ ).

252

253 Darrow et al [62] retrospectively evaluated the use of either BMC or whole bone marrow, injected into the joints  
254 and tendons of 18 subjects with RC tears. Participants were advised to perform daily shoulder stretches as part of  
255 their rehabilitation. They reported improved functional outcomes and pain scores for both groups but did not  
256 provide separate data or information on the size of tears and specific site of injection.

257

### 258 ***3.2.2 Bone Marrow Concentrate (BMC) and Adjunctive therapies***

259 Five studies reported on the use of BMC and other therapies. One study [64] reported on the use of BMC and  
260 adjunctive therapies in revision RC surgery and found functional scores that trended towards improvement,  
261 although for the most part these were not significant. Four studies[57–59,67] reported on the results of BMC and  
262 adjunctive therapies injected into RC tendon. All four studies reported improvements in functional scores  
263 following the injection of BMC and adjunctive therapies, two of which compared with a control group [57,67].  
264 No significant improvement in tear size was demonstrated compared to baseline[67] or control groups[57].

265

266 Muench et al[64]reported on the use of a biologically augmented patch saturated with a BMC/Platelet Rich  
267 Plasma (PRP) mix in 22 patients who required revision rotator cuff surgery. Patients were placed in a 30 degree  
268 abduction sling for at least 6 weeks. From day 28 postoperatively, patients were allowed 60 degrees of active  
269 assisted external rotation, 30 degrees of abduction and forward flexion from 30 to 180 degrees during physical  
270 therapy. Subsequently, patients were allowed to start active assisted range of motion in external rotation and

271 forward flexion without limitations until 12 weeks postoperatively. This was followed by RC strengthening until  
272 18 weeks. The Simple Shoulder Test (SST) scores improved from  $2.6 \pm 3.0$  pre-operatively to  $5.2 \pm 4.2$  post-  
273 operatively ( $p < 0.05$ ). The American Shoulder and Elbow Surgeon (ASES) score increased from  $40.2 \pm 21.6$  pre-  
274 operatively to  $53.9 \pm 31.4$  post-operatively, however statistical significance was not reached. The Visual  
275 Analogue Scale (VAS) pain scores decreased from  $5.6 \pm 2.5$  pre-operatively to  $4.2 \pm 3.4$ , again this did not reach  
276 statistical significance.

277

278 Centeno et al[58] reported on two distinct groups of patients, one with osteoarthritis and one with RC disorders.  
279 Improvements in the functional scores of patients who received intra-articular/intra-tendinous injections of a  
280 combination of BMC, PRP and Plasma Lysate (PL) were reported. No details regarding rehabilitation were  
281 available. The Disabilities of the Arm, Shoulder and Hand score (DASH) improved from 36.1 pre-treatment to  
282 17.1 post-treatment at an average follow-up of 7.1 months ( $p < 0.001$ ). Similarly, the numeric pain scale (NPS)  
283 improved from 4.3 pre-treatment to 2.4 post-treatment at a mean follow up of 8.3 months ( $p < 0.001$ ). However, the  
284 results were not separated between the RC group and the osteoarthritis group. When the two groups were  
285 compared, uni and multi-variate analysis showed no differences in outcomes.

286

287 Kim et al[57,59] published two studies reporting on 12 patients who had sub-acute partial rotator cuff tears. The  
288 initial study reported on 12 patients who had a BMC-PRP mixture injected into the site of their tear. In the second  
289 study, the patients from the initial group were compared to a control group who received physiotherapy alone. The  
290 experimental group had no rehabilitation, whilst the control group were shown RC exercises to perform for three  
291 months. After three months, the treatment group showed greater functional outcome improvements compared to  
292 the control group (VAS  $1.9 \pm 0.7$  and  $3.7 \pm 1.8$  respectively ( $p < 0.05$ ) and ASES  $74.1 \pm 8.5$  and  $62.2 \pm 12.2$  respectively  
293 ( $p < 0.05$ )). There were no significant changes in tear size between the two groups.

294

295 Centeno et al[67] performed a prospective RCT crossover trial with 14 patients in the treatment group receiving a  
296 BMC injection and a second group receiving exercise therapy. Patients were instructed to limit lifting and pushing  
297 and to perform passive range of motion exercises thrice daily up to day three post-procedure. From day three to  
298 week four, patients were encouraged to continue thrice daily range of motion exercises with the addition of  
299 pendulum, pulley exercises and shoulder girdle strengthening exercises. From weeks five to 11, patients were  
300 advised to start resistance training, and with no restrictions after week 12. They found significant improvements in

301 the Disabilities of the Arm, Shoulder and Hand (DASH) Score, Numerical Pain Scale and Single Assessment  
302 Numeric Evaluation (SANE) at all time points prior to crossover in favour of the BMC only group. At 24 months  
303 however there were no statistically significant differences in these variables between the BMC only group and the  
304 crossover group (exercise therapy with the opportunity to cross over at 3 months). Magnetic resonance imaging  
305 assessment of tears, by three blinded assessors, showed a mean decrease in size of 26% in the BMC group, which  
306 was not statistically significant.

307

### 308 **3.2.3 Mesenchymal Stem Cells**

309 Four studies evaluated the use of MSC. Three [60,61,63] studies reported on the injection of MSC. Functional  
310 scores increased in all studies, however significance was limited to high dose MSC [61,63] and was not reached  
311 compared to a control group of arthroscopic repair alone [60]. There was also a significant decrease in re-tears in  
312 the MSC treated group compared to the control group [60]. In the remaining study [68], MSCs were used to  
313 augment RC repair and, while functional scores increased in the treatment group, so too did the re-rupture rate.

314

315 Kim et al [60] reported on 35 patients treated with adipose derived MSC/fibrin glue injection compared with a  
316 control group of 35 patients undergoing surgical repair alone. Passive exercises were permitted from the day after  
317 surgery, whilst active exercises were not permitted until at least week six. Active assisted exercises were initiated  
318 six weeks after surgery alongside muscle-strengthening exercises. Manual labour or recreational activities were  
319 delayed for six months. The Constant score in the injection group improved from  $65.2 \pm 14.6$  pre-operatively to  
320  $78.3 \pm 14.9$  postoperatively ( $P < 0.001$ ). The UCLA score increased from  $26.5 \pm 5.2$  pre-operatively to  $29.8 \pm 5.1$   
321 post-operatively. This improvement did not reach statistical significance. There were no statistically significant  
322 differences between the UCLA scores and Constant score between both groups at final follow up. The VAS  
323 scores at rest and during motion also saw statistically significant improvements in both groups, with no difference  
324 between the groups. The structural outcomes of the injection group, as assessed by MRI at a mean of 13.9 months  
325 (12-21 months), showed 30 tears with complete healing, with a statistically significant reduction in numbers of re-  
326 tears (5 vs 10  $p < 0.001$ ). There was a statistically significant reduction of re-tears in patients who had full  
327 thickness tears (3 vs 9  $p < 0.001$ ).

328

329 Lamas et al [68] reported on eight patients using a xenogeneic scaffold augmented with bone marrow derived  
330 cultured MSC compared to a control group of five patients who received the scaffold alone. Post-operatively,

331 patients were placed in an abduction sling for a non specified duration. The trial was stopped early because of  
332 high complication rate. Of those who completed the study, five patients (62.5%) sustained a re-rupture in the  
333 MSC group compared to three patients (60%) in the control group. The Constant score improved from a mean of  
334 44.5 (30-63) pre-operatively to 72 (43-87) post-operatively and the VAS improved from 8.1 (7-9) pre-operatively  
335 to 2.9 (1-8) post-operatively in the MSC group.

336

337 Jo et al[61] divided 19 participants receiving an intra-tendinous injection of cultured adipose derived MSCs with  
338 saline alone into three dosage groups: low, medium and high. Post-injection, patients were immobilization for  
339 four weeks

340 in an abduction brace. Shrugging, protraction, and retraction of shoulder girdles; intermittent exercise of the  
341 elbow,

342 wrist, and hand; and external rotation of the arm to neutral with the brace were encouraged as tolerated. Gradual  
343 weaning from the abduction brace at four weeks with passive and active assisted range of motion exercises was

344 commenced and strengthening exercises thereafter. the 2-year follow-up results were published separately[63]:

345 eight bursal-side defects in the high-dose group had a 100% improvement in the defect size at 2 years. There was  
346 no statistically significant improvement in the four articular-side defects in the high dose group nor any of the  
347 bursal-side, articular-side or intra-tendinous defect sizes in the medium and low dose groups. Functional scores  
348 improved in all groups at final follow up, but these were mostly statistically significant in the high-dose group  
349 only.

350

#### 351 ***3.2.4 Mesenchymal Stem Cells and adjunctive therapies***

352 A single study evaluated the use of MSC in conjunction with other therapies.

353

354 Protzman et al [65]reported the findings of a case of recurrent RC tears where a dermal allograft combined with  
355 MSCs and PRP was used for surgical repair. The post-operative rehabilitation regime was not described. A biopsy  
356 taken 8 months post-operatively showed that the graft had become fully incorporated and had undergone tissue  
357 remodelling.

358

#### 359 ***3.2.5 Tenocytes***

360 The use of tenocytes was reported in two studies. Both studies [27,51] report improved tear size following the

361 injection of tenocytes.

362

363 Wang et al[66] theorised that the use of tenocyte-containing preparations may promote healing ‘through  
364 replenishing the depleted tenocyte population seen in end-stage tendinopathy’. They reported a single patient in  
365 whom autologous tenocytes were harvested from the patellar tendon and injected into a partial thickness tear.  
366 Following injection, the patient was rested from all training for four weeks. This was followed by light training  
367 and at 12 weeks the patient was allowed to return to full training. Two independent radiologists reported that the  
368 partial thickness supraspinatus tear was no longer detectable on MRI scan at 10 months post procedure. However,  
369 tendinopathy (as defined by tendon thickening with persistent focal signal increase) persisted at 10 month follow  
370 up.

371

372 Schwab et al [27]reported a patient in whom the subscapularis tendon was injected with tenocytes obtained from  
373 autologous palmaris longus tendon. Post-procedure, there was a period of three days of complete rest. This was  
374 followed by modified training in the pool at two and a half weeks, and full training over three to four weeks.  
375 Three blinded radiologists reported improvements in both tear size (judged by Walton criteria[69]) and  
376 tendinopathy.

377

### 378 ***3.2.6 Stromal Vascular Fraction***

379 Only one study reported the use of SVF.

380

381 Hurd et al [70]used adipose tissue from the abdomen, flank or inner thigh to obtain SVF for injection into the  
382 tendons of 12 patients. A control group of six patients received a corticosteroid injection into the subacromial  
383 space. Patients were advised to avoid overhead activities for the first two days, and continue with any home  
384 treatment programme already instigated. No further specific restrictions were placed. The American Shoulder and  
385 Elbow Surgeons scores improved from a baseline of  $58.7\pm 5.8$  to  $89.4\pm 4.9$  at 52 weeks post treatment in the SVF  
386 group compared to the steroid group which changed from  $50.6\pm 6.7$  at baseline to  $68.4\pm 4.4$  at 52 weeks post  
387 treatment ( $p<0.05$ ). The Short Form Survey 36 (SF-36), VAS and MRI appearances showed no statistically  
388 significant difference between the groups.

389

390

391 **3.2.7 Clinical outcomes**

392 The main clinical outcome scores used were the UCLA shoulder score, VAS pain score, ASES score and Constant  
393 score. The effect sizes are represented in Figures 3 and 4 for relevant studies excluding case reports. Five  
394 studies[57,59,60,68,70]reported on both pre- and post-intervention VAS scores. The average pre-intervention  
395 VAS was 4.8. This improved to 1.8 at a mean follow up of 11.7 months (3 – 28.3 months). Four  
396 studies[57,59,64,70] reported on the ASES score with an average score pre-intervention of 44.4.This improved  
397 post-intervention to an average of 72.3 at a mean follow-up of 12 months (3 – 30 months). Two studies reported  
398 on the UCLA shoulder score[55,60] and Constant score[60,68] respectively. The mean UCLA score pre-  
399 intervention was 19.3. This increased post-intervention to 30.4 at a mean follow up of 20.2 months (12 – 28.3  
400 months). The Constant score was a mean of 54.9 pre-intervention increasing to 75.2 post-intervention at a mean of  
401 20.2 months (12 – 28.3 months).

402

403 **3.2.8 Imaging outcomes**

404 Most of the studies reporting imaging outcomes used MRI as their imaging modality of choice. Five  
405 studies[57,59,61,67,70]reported a decrease in tear size at follow-up (two using ultrasound and three using MRI).  
406 Four studies[27,60,63,66] reported healing in 85.7% to 100% of patients. Two studies reported on tendon  
407 integrity, with Ellera-Gomes et al[55] reporting integrity in 100% of patients at 12 months and Heringou et al[56]  
408 reporting integrity in 87% of patients at 10 year follow-up.

409

410 **3.2.9 Complications**

411 Amongst the complications detailed in the studies, Heringou et al [56]report 6 re-tears between 2 and 4 years. The  
412 RCT by Lamas et al [68] was stopped early because of a high complication rate. In the treatment group, three  
413 patients developed lesions requiring further surgery. Additionally, the re-tear rate was 62.5% in the treatment  
414 group, another factor which hastened the cessation of the trial. Five patients required revision procedures at an  
415 average of 1.9 years in the study by Muench et al[64]. Additionally, one patient required excision of painful suture  
416 material and one patient sustained a deep infection.

417

418

419

420



421 **3.3 Elbow: Epicondylitis**

422 Six studies concerning the use of cell-based therapies in epicondylitis were identified. One involved augmenting  
423 surgical treatment, the others reported results following intra-tendinous injections of cell-based preparations into  
424 the lateral epicondyle.

425

426 **3.3.1 Bone Marrow Concentrate**

427 Two studies reported on the use of BMC. Both studies report improved functional scores following surgical  
428 debridement [49] or in isolation [52].

429

430 Moon et al[49] investigated the use of autologous BMC injections in 26 elbows with epicondylitis (24 patients).

431 The patients received a dose of BMCs with bupivacaine immediately following arthroscopic debridement of  
432 degenerative tissue within the common extensor origin. The elbow was immobilised in a splint for 2 days, active  
433 resistance exercises started at 6 weeks post operatively, and more vigorous exercise allowed after two to three  
434 months. At 6 months follow up, patients had significant improvements in VAS (7 at baseline improving to 1.7)  
435 and Mayo Elbow Performance Score (MEPS) ( $52 \pm 7.6$  at baseline improving to  $89 \pm 7.9$ ,  $p < 0.001$ ).

436

437 Singh et al[52] examined the use of BMC injection without operative treatment in 26 patients with lateral  
438 epicondylitis. Post-injection, patients were advised to rest and modify their activities. Patient-rated Tennis Elbow  
439 Evaluation (PRTEE) scores improved from  $72.8 \pm 7.0$  at baseline to  $14.86 \pm 3.5$  at 3 months ( $p < 0.0001$ ).

440

441 **3.3.2 Mesenchymal Stem Cells**

442 One study reported the use of MSC.

443

444 Lee et al[53] investigated injection of allogenic adipose-derived cultured MSCs and fibrin glue into the common  
445 extensor origin. Twelve participants were split into two groups, a low dose group and a high dose group. No  
446 specific rehabilitation was instigated post injection. The VAS improved from a baseline of  $66.8 \pm 14.5$  to  $14.8 \pm$   
447  $13.1$  at 1 year. Similarly, the MEPS improved from a baseline of  $64 \pm 13.5$  to  $90.6 \pm 5.8$  at 52 weeks. The  
448 appearances of tendinous defect on ultrasound were also found to have significantly decreased at 52 weeks.

449

450

451 **3.3.3 Tenocytes**

452 Three studies reported on the use of tenocytes. All studies [50,51,54] demonstrated improved functional scores  
453 and appearances on imaging following injection of tenocytes.

454

455 Wang et al reported two studies[51,54], the first of which included 16 patients injected with patellar tendon  
456 derived tenocytes. Patients were advised to rest for 2 days post injection and then perform only light activities for  
457 four weeks. Additionally, advice regarding four times daily forearm extensor muscle stretches was given. Visual  
458 Analogue Scale scores improved from  $5.9 \pm 2.2$  at baseline to 0.8 (no standard deviation provided) at 12 months.  
459 The QuickDASH score improved from  $45.88 \pm 15.2$  at baseline to  $2.88 \pm 0.7$  at final follow-up ( $P < 0.001$ ). The  
460 MRI appearances of the tendon were also significantly improved at 12 months. In the second study, the same  
461 cohort was followed to 4.5 years. The QuickDASH was  $6.61 \pm 1.9$  at final follow up and VAS was  $1.21 \pm 0.3$  at  
462 final follow up.

463

464 Connell et al[50] performed a similar study using tenocyte-like cells derived from skin fibroblasts. In this study  
465 cells were injected into the lateral epicondyle of 12 patients. Patients were advised to limit the use of the injected  
466 arm for 24 hours after which normal activity could resume bar heavy lifting. The PRTEE score improved from a  
467 baseline of 78 (71 – 88) to a median of 12 (0 – 25) at 6 months ( $p < 0.05$ ). Assessment of tendons using  
468 ultrasonography at 6 months showed improvement in appearance ( $p < 0.05$ ).

469

470 **3.3.4 Clinical outcomes**

471 The PRTEE, VAS and MEPS were the most commonly used functional scores. The effect sizes are represented in  
472 Figure 5 for relevant studies excluding case reports. Three studies[49,53,71] reported on the VAS; at baseline, the  
473 mean VAS was  $6.5 \pm 0.5$ , improving to  $1.5 \pm 0.2$  at an average 24 months (6 – 54.1 months) follow-up. Two  
474 studies[49,53]reported on the PRTEE score. At baseline, the mean score was  $75.4 \pm 2.6$ , which improved to  $13.4$   
475  $\pm 1.4$  at an average of 4.5 months (3 – 6 months) follow up. Two studies[49,53] reported on the MEPS, with a  
476 baseline of 58 improving to 89.8 at a mean follow-up of 9 months (6 – 12 months).

477

478 **3.3.5 Imaging outcomes**

479 Four studies reported on imaging outcomes post intervention. Two studies[50,53] reported improved defect size  
480 and appearances tending towards normality at 6 months and 12 months, respectively. Two studies from Wang et

481 al [51,71] reported on the MRI appearance of the tendon. Both showed improved appearances at 12 months, and  
482 these improvements were maintained at 5 years.

483

#### 484 **3.3.6 Complications**

485 Of the studies reported, there was only one reported complication. In the pilot study by Wang et al[51], one  
486 patient exhibited worsening of the appearances of the tear post intervention. The deterioration resulted in the need  
487 for surgical intervention. No further complications were reported in any of the studies.

488

#### 489 **4. Conclusion**

490 Within the limitations of this study, tenocytes have shown the most promise in the management of epicondylar  
491 tendinopathy. In the studies that used tenocytes, both clinical and imaging scores improved, with imaging  
492 improvements maintained at up to five years follow-up. In the management of rotator cuff pathology, BMC  
493 showed the most promising results when used in isolation or as an adjunct to surgical repair. The studies using  
494 BMC evidenced improvements in functional scores and fewer complications.

495

496 In the non-randomised studies, the magnitude of effect of intervention on clinical scores was mostly large,  
497 suggesting that patient scores are likely to show meaningful improvements following treatment with cell-based  
498 therapies. However, in the RCTs, the effect magnitude of cell-based therapies was only small to medium. This  
499 highlights the need for further high-quality randomized studies to establish whether the use of cell-based therapies  
500 truly results in improved patient outcomes.

501

502 Whilst there are many promising findings reported in the included studies, a lack of standardization in methods,  
503 culture and cell type make firm conclusions difficult to draw. We suggest that future studies should focus on  
504 establishing techniques to reliably identify cell type and number. This would lay the foundations for greater  
505 comparability of studies, and enable direct comparison of outcome measures. It is also imperative that the  
506 outcomes measured focus on patient pain, function and quality of life. To this end, we suggest that PROMs should  
507 be the primary outcome measure of future studies. Whilst imaging evidence of tendon integrity is a useful metric  
508 of the regenerative abilities of cell-based therapies, if this is not accompanied by improvements in a patient's  
509 function, pain or quality of life, the usefulness of these therapies as a suitable treatment would understandably be  
510 questioned.

511 **5. Expert Opinion**

512 Twenty two studies were included in this systematic review, of which only three were of level 1 evidence [72].  
513 Three of the studies were RCTs, all of which pertained to the treatment of rotator cuff injuries. There were mixed  
514 results with regards to clinical outcomes, with some showing no significant difference between treatment and  
515 control groups. However, most functional scores were significantly better in the treatment groups compared to the  
516 control group. None of the studies reported serious adverse effects as a result of the cell-based treatment.  
517 However, Lamas et al [68] terminated their study early due to a number of complications in both treatment and  
518 control groups which they attributed to the scaffold used.

519  
520 It was not possible to conduct a meta-analysis of the available data in any of the sections due to the heterogeneity  
521 between studies. Studies varied greatly in the type of cell-based therapy used, in their functional and imaging  
522 outcomes and their intervals of measurement/follow up (Table 1). The wide variety in the reporting of methods  
523 and in the cell amounts make replication and standardization of studies difficult to achieve [73]. However,  
524 assessment of effect sizes was possible (Figures 3-5). In the three RCTs [57,68,70] included in this study, with the  
525 exception of VAS score in the study by Lamas et al [68], the effect sizes favoured the intervention group.  
526 However, with the exception of the ASES score in Kim et al [57] at 3 months, which showed a large effect, the  
527 remaining studies showed at best a medium effect. For these studies, the confidence intervals suggest that, whilst  
528 the majority of patients might see a favourable response following surgery, there will also be a proportion of  
529 patients who do not respond as well, or indeed, at all (Figure 3).

530  
531 In the non-randomised studies of rotator cuff injuries, UCLA and VAS scores showed large effect sizes, with the  
532 confidence intervals indicating all patients could expect to experience improvement as a result of intervention.  
533 However whilst Kim et al [59] demonstrated a large effect for the ASES score, Muench et al [64] demonstrated  
534 only a small effect. Considering both these studies, the data would suggest that the majority of patients would  
535 experience a meaningful improvement in this outcome following intervention, but some may not respond so well.  
536 In the non-randomised studies of epicondylitis, large effect sizes were demonstrated for all clinical scores, with  
537 confidence intervals suggesting that all patients should achieve a meaningful response to intervention (Figure 5).  
538 This would indicate that cell-based therapies used for the management of epicondylitis would result in  
539 improvement in clinical scores for all patients. Whilst these results are promising, given the lack of  
540 randomization, they should be interpreted with a degree of caution.

541

542 The use of effect sizes in this study has highlighted the issue of responders and non-responders to treatments. This  
543 issue in any therapy, not just a biological therapy, is very much to the forefront in musculoskeletal medicine [74]  
544 and In these days of personalised medicine, this is an issue which needs to be taken into account. However, to our  
545 knowledge this approach, though desirable and scientifically valid, has not been taken when planning  
546 investigations in this field. It is extremely likely that, although it would make sense to stratify patients according  
547 to their intrinsic capability and propensity to respond to a given therapeutic intervention, the practicalities and  
548 costs of such approach would be prohibitive.

549

550 Serious complications related to the use of cell-based therapies are rare [40], with the majority of complications  
551 reported being limited to pain related to route of administration [86]. Amongst the studies included in this review  
552 there was a low rate of complications, with none being directly attributed to the use of cell-based therapies.

553

554 The standardization of cell-based therapies would enable greater comparability of studies, and also allow the  
555 utilization of demonstrably successful techniques to improve patient care. Unfortunately, given the complexity in  
556 the heterogeneity of the cells and the variability in their procurement, this is unlikely to happen in the near future  
557 [87]. The American Academy of Orthopaedic Surgeons (AAOS) have suggested methods for achieving greater  
558 standardization which include everything from nomenclature to the source and preparation of MSC [73,88].  
559 However, until a global consensus is reached, it is unlikely that advances in the field will be reproducible on a  
560 large scale. One recently developed reporting tool, which reached a consensus using a modified Delphi method, is  
561 the DOSES tool [89]. This tool implores the researcher to report the Donor, Origin tissue, Separation method,  
562 Exhibited cell characteristics and Site of delivery of the cell-based therapy used. By utilising reporting tools like  
563 DOSES, it is hoped that the transparency and standardisation of cell-based therapies can be achieved. This would  
564 allow for a greater understanding of the preparations and once their efficacy were established, allow greater  
565 reproducibility in their clinical applications.

566

567 The potential for cell-based therapies in the management of sports injuries is limitless. In the future, in select  
568 cases, cell-based therapies may eliminate the need for the surgical management of common sports injuries, thus  
569 removing an element of risk. With a move towards standardisation of reporting and greater regulation of cell-  
570 based therapies, it is likely that they will become more widely available and, with this, the ability to conduct high

571 quality and more readily reproducible studies will also increase.

572

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576

577 **Conflicts of interest/Competing interests**

578 The authors declare that the research was conducted in the absence of any commercial or financial relationships

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580

581 **Availability of data and material**

582 The authors declare that all data supporting the findings of this study are available within the article

583

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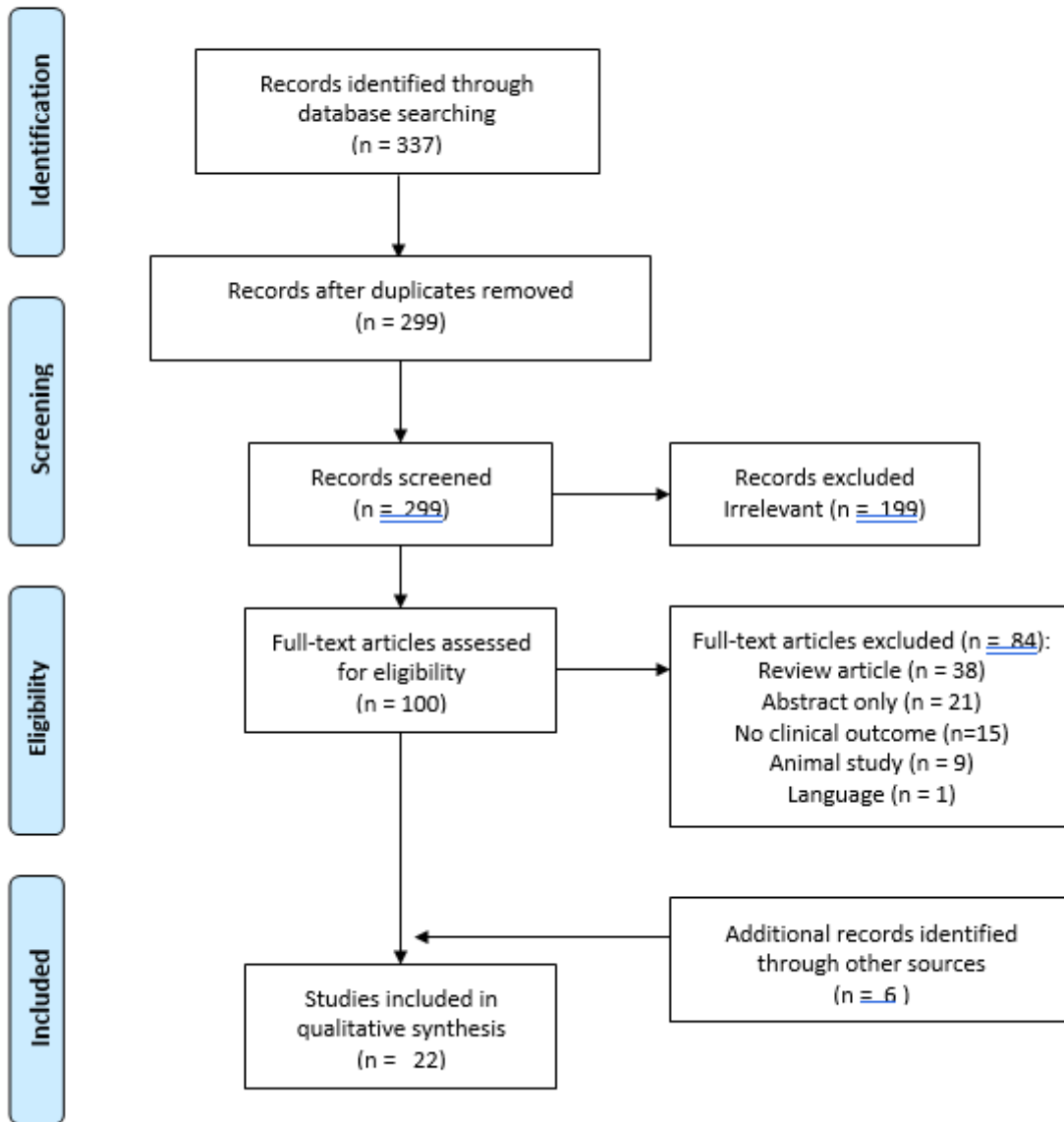
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**PRISMA 2009 Flow Diagram**



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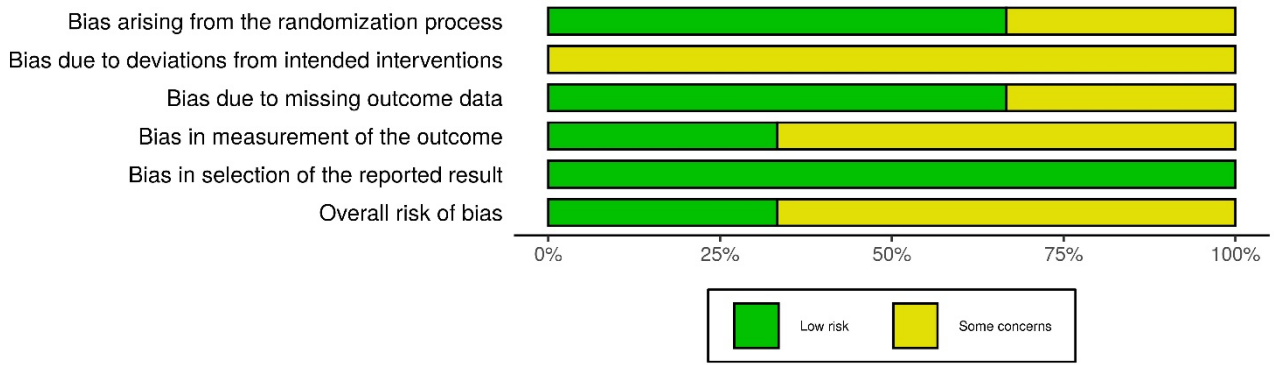
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849 **Figure 2**



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853 **Figure 3**

854 **SHOULDER - RCT**

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**VAS**

Kim SJ et al (2018) at 3 weeks  
Kim SJ et al (2018) at 3 months  
Lamas et al (2019) at 12 months  
Hurd et al (2020) at 24 weeks  
Hurd et al (2020) at 52 weeks

**ASES**

Kim SJ et al (2018) at 3 weeks  
Kim SJ et al (2018) at 3 months  
Hurd et al (2020) at 24 weeks  
Hurd et al (2020) at 52 weeks

**Constant**

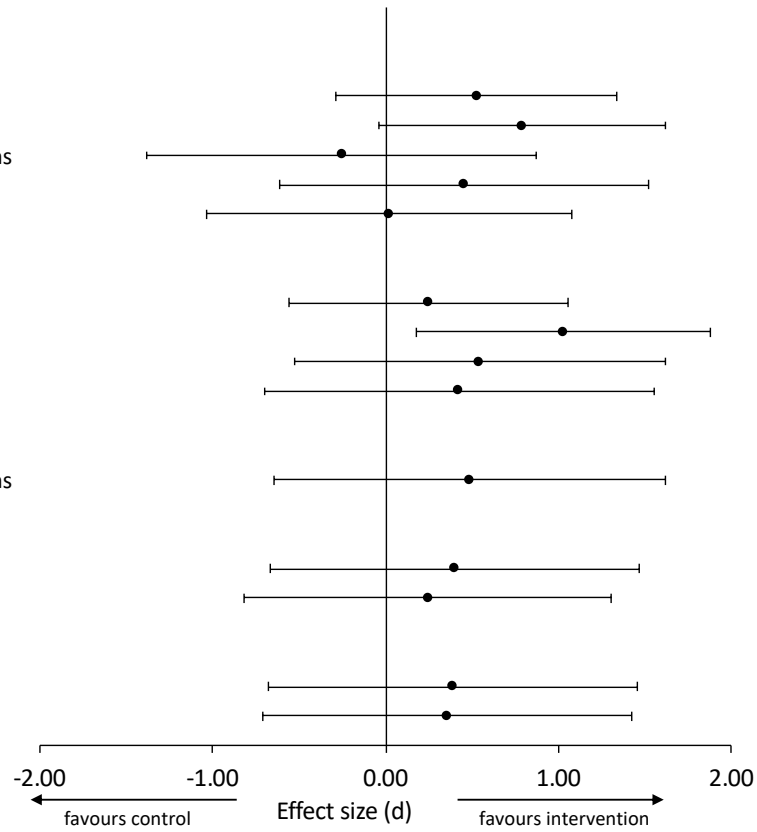
Lamas et al (2019) at 12 months

**SF-36**

Hurd et al (2020) at 24 weeks  
Hurd et al (2020) at 52 weeks

**Tear Size**

Hurd et al (2020) at 24 weeks  
Hurd et al (2020) at 52 weeks



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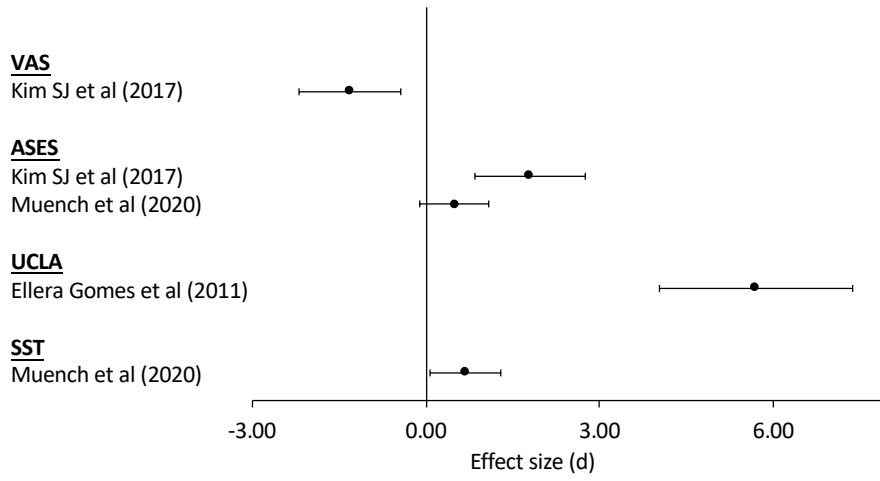
Figure 3. Hedges *d* effect sizes are shown for the pre-post mean difference in each outcome between intervention and control groups for randomised controlled trials of the shoulder. 95% confidence intervals are shown.

861 **Figure 4**

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863 **SHOULDER**

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866 *Figure 4. Hedges d effect sizes are shown for the pre-post mean difference in each outcome between*  
867 *intervention and control groups for non-randomised controlled trials of the shoulder. 95% confidence*  
868 *intervals are shown.*

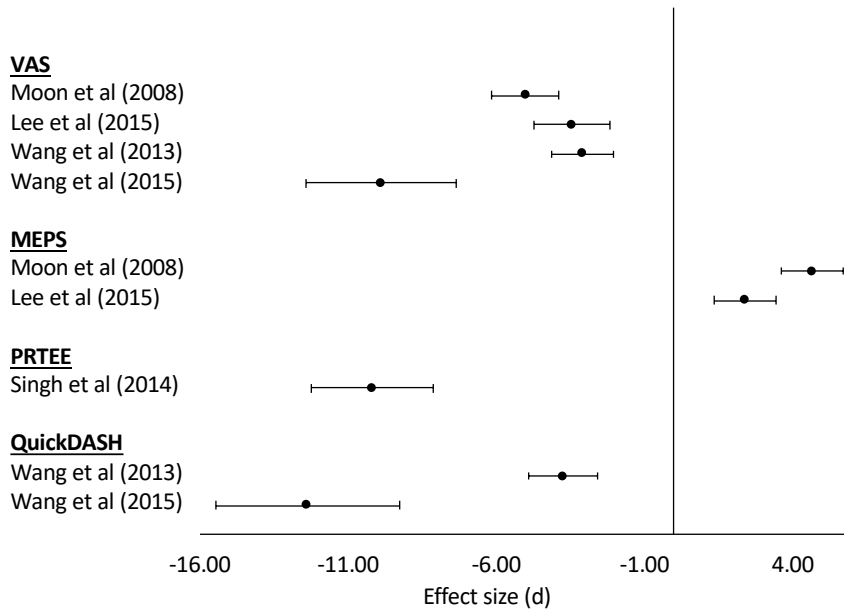
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870 **Figure 5**

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872 **ELBOW**

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875 *Figure 5. Hedges d effect sizes are shown for the pre-post mean difference in each outcome between*  
876 *intervention and control groups for non-randomised controlled trials of the elbow. 95% confidence intervals*  
877 *are shown.*

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880 **Table 1 – Study characteristics and levels of evidence**

Author/Year	Study Design	Patients Treated (n)	Follow up period	Diagnosis	Intervention	Biologic(s) used	Cell source	Number of cells	Comparator	Level of Evidence
Moon 2008	Case series	24	6 months	Epicondylitis	Injection	BMC	Iliac spine	Not stated	None	Level 4
Connell 2009	Case Series	12	6 months	Epicondylitis	Ultrasound guided injection	Tenocytes	Hip	10 x 10 <sup>6</sup>	None	Level 3
Ellera Gomes 2011	Case series	14	12 months	Rotator Cuff tear	Augmented Rotator cuff repair	BMC	Iliac Crest	CD34+: 5.65 x 10 <sup>6</sup> MNC: 3.81 x 10 <sup>8</sup>	None	Level 4
Protzman 2013	Case Report	1	8 months	Rotator cuff re-tear	Patch augmented rotator cuff repair	MSC and PRP	Not stated	Not stated	None	Level 5
Wang 2013	Case series	16	12 months	Epicondylitis	Ultrasound guided injection	Tenocytes	Patella tendon	2-5 x 10 <sup>6</sup>	None	Level 4
Wang 2013	Case report	1	10 months	Rotator cuff tear	Ultrasound guided injection	Cultured tenocytes	Patella tendon	2 x 10 <sup>6</sup>	None	Level 5
Hernigou 2014	Case control	45	24 months	Rotator cuff tear	Augmented Rotator cuff repair	BMC	Iliac crest	5.1 x 10 <sup>4</sup>	45 patients with repair without BMC	Level 3
Singh 2014	Case series	30	3 months	Epicondylitis	Injection	BMC	Iliac spine	Not stated	None	Level 4
Centeno 2015	Retrospective Cohort study	81	Unclear	Rotator cuff tear	Ultrasound guided injection	BMC, PRP and plasma lysate	Iliac crest	4.99 x 10 <sup>8</sup>	34 patients with Osteoarthritis	Level 3
Lee 2015	Case series	12	12 months	Epicondylitis	Ultrasound guided injection	MSC	Not stated	Not stated	None	Level 4
Wang 2015	Case series	16	4.51 years*	Epicondylitis	Ultrasound guided injection	Tenocytes	Patella tendon	2-5 x 10 <sup>6</sup>	None	Level 4

Kim SJ 2017	Single blind study	12	3 months	Rotator cuff tear	Ultrasound guided injection	BMC and PRP	Iliac crest	Not stated	None	Level 2
Kim YS 2017	Cohort study	35	28.3 months*	Rotator cuff tear	Augmented rotator cuff repair	MSC	Buttock	4.46 x 10 <sup>6</sup>	35 patients with repair without MSC	Level 3
Jo 2018	Cohort study	19	6 months	Rotator cuff tear	Ultrasound guided injection	MSC	Abdomen	Low - 1.0x 10 <sup>7</sup> Mid -5.0 x 10 <sup>7</sup> High - 1.0 x 10 <sup>8</sup>	None	Level 2
Kim SJ 2018	Case control	12	3 months	Rotator cuff tear	Ultrasound guided injection	BMC and PRP	Iliac crest	Not stated	12 patients with exercise programme	Level 2
Schwab 2018	Case report	1	18 months	Rotator cuff tear	Ultrasound guided injection	Tenocytes	Palmaris Longus tendon	5 x 10 <sup>6</sup>	None	Level 5
Darrow 2019	Retrospective Cohort study	18	7.54 months*	Rotator cuff tear	Ultrasound guided injection	BMC	Iliac crest	Not stated	32 patients with osteoarthritis	Level 3
Lamas 2019	Randomised controlled trial	8	12 months	Rotator cuff tear	Patch augmented rotator cuff repair	MSC	Iliac spine	Not stated	5 patients with patch augmented repair without BMC	Level 1
Centeno 2020	Randomised controlled crossover study	14	24 months	Rotator cuff tear	Ultrasound guided injection	BMC, PRP and plasma lysate	Iliac crest	8.96 x 10 <sup>6</sup>	11 patients treated with exercise	Level 1
Hurd 2020	Randomised controlled trial	12	12 months	Rotator cuff tear	Ultrasound guided injection	SVF	Abdomen, flank or thigh	11.4 x 10 <sup>6</sup>	6 patients treated with steroid injection	Level 1
Jo 2020	Retrospective Cohort study	19	24 months	Rotator cuff tear	Ultrasound guided injection	MSC	Abdomen	Low - 1.0x 10 <sup>7</sup> Mid -5.0 x 10 <sup>7</sup> High - 1.0 x 10 <sup>8</sup>	None	Level 3

Muench 2020	Retrospective Cohort study	22	2.5 years*	Rotator cuff re-tear	Patch augmented rotator cuff repair	BMC and PRP	Humerus	24 x 10 <sup>6</sup>	None	Level 3
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\* = mean follow up

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BMC = bone marrow concentrate; MSC = mesenchymal stem cells; PRP = platelet rich plasma

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886 **Table 2**

		Risk of bias domains					
		D1	D2	D3	D4	D5	Overall
Study	Lamas 2019						
	Hurd 2020						
	Centeno 2020						

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Domains:

D1: Bias arising from the randomisation process

D2: Bias due to deviations from intended interventions

D3: Bias due to missing outcome data

D4: Bias in measurement of the outcome

D5: Bias in selection of the reported result

Judgement

Some Concerns

Low

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**Table 3 – Risk of Bias assessments using AHRQ tool**

Author	Selection Bias	Performance Bias	Attrition Bias	Detection Bias	Reporting Bias	Study type
Moon 2008	*	*	*	**	*	Case series
Connell 2009		*	*	**	*	Case series
Ellera Gomes 2011		*	*	**	*	Case series
Wang 2013		*	*	**	*	Case series
Hernigou 2014	**	**	*	***	*	Case control
Singh 2014		*	*	*	*	Case series
Centeno 2015	**		*	***	*	Cohort Study
Lee 2015	*	*	*	**	*	Case series
Wang 2015		*	*	**	*	Case series
Kim SJ 2017	***	*	*	****	*	Cohort Study
Kim YS 2017	****	*	*	***	*	Cohort Study
Jo 2018	**	*	*	***	*	Cohort Study
Kim SJ 2018	*		*	***	*	Case control
Darrow 2019	***	*	*		*	Cohort Study
Jo 2020	**	*	*	***	*	Cohort Study
Muench 2020	***	*		***	*	Cohort Study

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896 Cohort studies – maximum of 13 stars

897 Case-control studies – maximum of 11 stars

898 Case series – Maximum of 9 stars