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PII: S0749-8063(20)30456-4

DOI: https://doi.org/10.1016/j.arthro.2020.05.037

Reference: YJARS 56976

To appear in: *Arthroscopy: The Journal of Arthroscopic and Related Surgery*

Received Date: 24 January 2020

Revised Date: 21 April 2020

Accepted Date: 17 May 2020

Please cite this article as: Maheshwer B, Polce EM, Paul K, Williams BT, Wolfson TS, Yanke A, Verma NN, Cole BJ, Chahla J, Regenerative Potential of Mesenchymal Stem Cells for the Treatment of Knee Osteoarthritis and Chondral Defects: A Systematic Review and Meta-Analysis, *Arthroscopy: The Journal of Arthroscopic and Related Surgery* (2020), doi: https://doi.org/10.1016/j.arthro.2020.05.037.

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**Running Title:**
Systematic Review of MSCs to treat Knee OA

# Regenerative Potential of Mesenchymal Stem Cells for the Treatment of Knee Osteoarthritis and Chondral Defects: A Systematic Review and Meta-Analysis

## ABSTRACT

**Purpose:** The purpose of this study is to perform a systematic review and meta-analysis evaluating the effects of mesenchymal stem cells on cartilage regeneration and patient-reported pain and function.

**Methods:** A systematic review was conducted according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines using a PRISMA checklist. The Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, PubMed (2008-2019), EMBASE (2008-2019), and MEDLINE (2008-2019) were queried in July 2019 for literature reporting use of stem cells to treat knee osteoarthritis or chondral defects. Data describing administered treatment, subject population, injection type, duration of follow-up, pain and functional outcomes, radiographic and MRI findings were extracted. Risk of bias was assessed using the Downs and Black scale. Meta-analyses adjusted for random effects were performed, calculating pooled effect sizes in terms of patient-reported pain and function, cartilage quality, and cartilage volume.

**Results:** Twenty-five studies with 439 subjects were identified. There was no significant difference in pain improvement between MSC treatment and controls (pooled standardized mean difference (SMD) = 0.23, p=0.30). However, MSC treatment was significantly favored for functional improvement (SMD = 0.66, p<0.001). There was improvement in cartilage volume after MSC treatment (SMD = 0.84, p<0.001). Regarding cartilage quality, meta-analysis resulted in a small, non-significant effect size of 0.37 (95%, -0.03 – 0.77, p=0.07). There was risk for potential bias among included studies, with 17 (68%) receiving either a grade of “poor” or “fair”.

**Conclusion:** The pooled standard mean difference from meta-analyses showed statistically significant effects of MSC on self-reported physical function but not self-reported pain. MSCs provided functional benefit only in patients who underwent concomitant surgery. However, this must be interpreted with caution as there was substantial variability in MSC composition and mode of delivery. MSC treatment provided significant improvement in cartilage volume, but not cartilage quality. Preliminary data regarding therapeutic properties of MSC treatment suggest significant heterogeneity in the current literature and risk of bias is not negligible.

**Level of Evidence:** II, Systematic Review and Meta-analysis

## INTRODUCTION

Osteoarthritis (OA) is one of the most frequent reasons for adult medical office visits, and one of the most common causes of joint pain and disability, with over 30 million symptomatic adults in the United States.[5] The healthcare cost of OA continues to grow due to increased patient longevity and rising prevalence of obesity. In 2013, the combined cost of medical care and lost wages due to OA exceeded $300 billion.[36, 48] Currently, the mainstays of nonoperative treatment include activity modification, physical therapy, non-steroidal anti-inflammatory drugs, and intraarticular injections of corticosteroid or hyaluronic acid. Unfortunately, none of these treatment options slow or reverse the progression of cartilage degeneration.

Mesenchymal stem cells (MSCs) have been extensively studied as a promising solution to alleviate symptomatic knee OA through pleiotropic effects on the local environment.[40] Attractive therapeutic properties of MSCs include immunosuppressive activity, multilineage potential, and a simple growth process in vitro.[56] MSCs also exhibit paracrine effects, which may impart therapeutic benefit even in the absence of tissue-specific differentiation.[9] Several meta-analyses have evaluated the efficacy of MSCs in the treatment of OA and chondral defects, focusing on the impact of MSCs on psychometric measures of pain and physical function. [8, 18, 56, 57, 58] Although these studies help validate the use of stem cells for clinical use, limited research has investigated the effect of MSCs on structural cartilage changes in this population. Furthermore, the potential for bias in assessing MSC effect on cartilage regeneration is likely to be high due to heterogeneity in study methodologies and treatment response due to challenges in blinding and randomization.

Multiple metrics have been described to evaluate cartilage quality and quantity, including the magnetic resonance observation of cartilage repair tissue (MOCART),[32] whole-organ magnetic resonance imaging score (WORMS),[41] and T2 mapping values.[51] A recent meta-

analysis reported the effect of MSC treatment on cartilage volume and quality; however, this study only analyzed changes in cartilage morphology in MSC treatment groups alone.[18]

Therefore, the purpose of this systematic review is to perform a systematic review and meta-analysis evaluating the effects of mesenchymal stem cells on cartilage regeneration and patient-reported pain and function. It was hypothesized that treatment of knee OA and chondral defects with MSCs would result in significant improvements in patient-reported pain and function, with limited improvement in cartilage regeneration (i.e., cartilage volume and quality) relative to controls.

## METHODS

*Article Identification and Selection*

This study was conducted in accordance with the 2009 Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement.[34] The Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, PubMed (2008-2019), EMBASE (2008-2019), and MEDLINE (2008-2019) were queried in July 2019 for literature reporting on the use of stem cells to treat osteoarthritis or chondral defects of the knee. Database queries were performed using the following Boolean search terms: knee AND osteoarthritis AND cartilage AND (stem cells OR stromal cells OR transplantation). Inclusion criteria were all studies with level of evidence I or II concerning stem cell use in treating osteoarthritis or knee chondral defects. Studies that were level of evidence three or greater were excluded. Studies investigating effects of stem cell treatments without adequate number of cell counts we excluded (i.e. bone marrow aspirate concentrate, BMAC). Additionally, studies with inadequate study design, blinding, or randomization were excluded. Two investigators (*blinded for review*) independently screened articles sequentially based on title, followed by abstracts, and finally full text, when appropriate. Full-text articles were reviewed if further assessment of inclusion and exclusion criteria was required. All references from included studies were screened to identify additional articles absent from the primary query. Systematic review registration was submitted in July 2019 for review by the PROSPERO International prospective registrar of systematic reviews.

*Outcome Measures and Data Extraction*

The primary outcomes evaluated in this systematic review were a) self-reported pain, b) self-reported physical function, and c) structural changes in articular cartilage (i.e., cartilage volume and quality) assessed via MRI. A customized spreadsheet including a modified information extraction table was created to record all relevant data from the included studies,

including publication information, study design (i.e., prospective cohort studies, non-randomized comparative studies, and randomized controlled trials (RCTs)), level of evidence, treatment, subject population, treatment details, duration of follow-up, pain and functional outcome measures, and radiographic and MRI findings. All data was analyzed qualitatively using descriptions of study methods, results, and conclusions. Articles reporting outcomes using multiple pain and function scales were assessed according to the psychometric outcome hierarchy detailed previously in the literature.[7, 17, 30, 33]

*Risk of Bias Assessment*

Two investigators (*blinded for review*) independently assessed risk of bias using the Downs and Black scale.[11] Disagreements between raters were resolved by consensus. Briefly, this numerical scale is comprised of 27 questions, including quality of reporting (ten questions), external validity (three questions), internal validity (bias and confounding, 13 questions), and statistical power (one question). Originally, the score was out of 32 possible points with the statistical power question having a maximum of five points. However, in accordance with previous studies, a simplified scale was used in which statistical power received a maximum of one point if sufficiently powered to detect a meaningful difference.[35, 42, 45] The modified Downs and Black scale was used to assign each included article a categorical grade of “excellent” (24-28 points), “good” (19-23 points), “fair” (14-18 points), or “poor” (<14 points).[37]

*Statistical Analysis*

For the meta-analyses, pooled estimates of effect sizes were calculated using a random effects model for the primary outcomes of self-reported pain and physical function, and cartilage structural changes. Standardized mean differences (SMD) and 95% confidence interval (CI) were used to assess outcome improvement from baseline to the longest follow-up time point, comparing subjects receiving MSCs and controls. For outcomes measured with different

assessment tools, such as self-reported physical function and cartilage quality, individual studies in the meta-analyses were grouped according to scoring metric.[18] The magnitude of the SMD was assessed according to Cohen's d estimate.[6] Briefly, <0.5, 0.5-0.8, and >0.8 correspond to small, medium, and large effect sizes, respectively. Considering the clinical interpretation of SMD is often ambiguous, mean differences in change (pre-to-post delta score) between MSC and control cohorts for the primary outcomes were also calculated and compared to established values of minimum clinically important difference (MCID). Study heterogeneity was assessed with I-squared ($I^2$) tests. Furthermore, sensitivity analyses were performed to explore the effects of MSC administration through computation of pooled SMD for outcome data from studies with MSC administered via injection and MSC administered concomitantly with a surgical intervention (as this could act as a confounding factor). Statistical analyses were performed utilizing Review Manager 5 (The Nordic Cochrane Center, Copenhagen, Denmark).[1]

## RESULTS

*Study Characteristics*

The database query yielded a total of 3,585 studies, of which 25 studies satisfied all pre-specified inclusion criteria. Because of extensive cross referencing and confirmation that no study data was replicated in included studies, there was no potential for duplicate data on the same patients across studies. Study characteristics of all studies, including those not used for meta-analyses, are described in **Table 1a and 1b**. Of the 25 included level I and II studies, three (12%) had a single-arm, prospective design, nine (36%) had a non-randomized comparative study design, and thirteen (52%) were RCTs. Dose-escalation studies were categorized as RCTs or non-randomized comparative studies depending on study design. A total of 489 subjects across the included studies received MSC treatment for osteoarthritis or chondral defects of the knee. The mean age of treatment subjects was 54.4 ± 7.2 years (range, 29.0-77.0 years). Seventeen studies (65%) included control arms, with a reported mean age of 53.4 ± 7.1 years (range, 18.0-70.0 years). Seventeen studies reported sex distributions for the treatment group (n = 440), with 269 female treatment subjects (61%). Fourteen studies reported sex for the control group (n = 320), with 216 female subjects (68%). Radiographic grading of knee osteoarthritis using the Kellgren-Lawrence scale (K-L) was reported in 22 studies (85%) with included K-L grades of 0-VI, with variable exclusion criteria across studies. Overall length of final follow-up ranged from one week to 100 months with a mean of 8.3 years. Treatments implemented in study groups included autologous and allogenic intra-articular MSC injection,[3, 4, 12, 15, 16, 19, 21, 22, 27-29, 38, 39, 46, 47, 52-54] matrix-induced MSC implantation,[2] MSC with platelet-rich plasma (PRP),[24-26] high tibial osteotomy (HTO) with MSC injection[23, 55], MSC implantation on

fibrin glue scaffold,[24] and cell-based biologics.[15, 31] Descriptions of cell therapies used in all included studies are listed in **Table 2.**

*Risk of Bias Assessment*

The Downs and Black score and categorical grade for the included studies is displayed in Table 1. The mean total score for all 25 studies was 16.3 ± 3.7 (range, 9-22); 9.2 ± 1.5 for quality of reporting, 3.7 ± 1.0 for internal validity (bias), 3.2 ± 1.6 for internal validity (confounding), and 0.2 ± 0.4 for statistical power. None of the included studies received points in terms of external validity due to an inadequate discussion of generalizability. Of the 25 studies, six (24%) received a categorical grade of "poor", 11 (44%) studies were "fair", eight (32%) studies were "good", while no studies attained a grade of "excellent". The mean score stratified by study design was 17.0 ± 1.7 for single-arm, prospective studies; 14.4 ± 3.5 for non-randomized, comparative studies; and 17.4 ± 3.8 for RCTs. There were no statistically significant differences between the stratified group means as determined by one-way ANOVA ($F = 1.87$, $p = 0.18$). The primary potential sources of bias for non-RCTs were lack of randomization, lack of a priori power analysis or insufficient power to detect a statistical difference, and inadequate blinding of subjects and study staff to the intervention assignment.

*Outcome Measures*

*Self-reported Knee Pain*

Nine studies assessed the effect of MSC treatment on knee pain via the visual analog scale (VAS). Of these, six studies (ten data sets, n = 312) compared improvement between MSC treatment and control groups. The mean follow-up time for these six studies was 16.9 ± 6.0 months (range, 12-24.4 months). Considering all six studies, the meta-analysis resulted in a pooled standardized mean difference (SMD) of 0.23 (95% confidence interval (CI), -0.20 — 0.65) (**Figure 2**). However, this value was not statistically significant (p=0.30), indicating no

significant difference in pain improvement between MSC treatment and control groups. Estimates of effect sizes were moderately heterogenous ($I^2$ = 70%).

To investigate if effect size and heterogeneity estimates vary based on surgical intervention, a sub-analysis stratifying studies based on whether studies administered MSC via injection only versus with a surgical adjunct (i.e. surgical administration of MSC or MSC administration with concomitant surgical procedure) was performed. The mean follow-up time of studies assessing MSC injection (12.0 ± 0 months) and MSC as surgical adjunct (21.7 ± 4.3 months) was significantly different (p=0.02). Study heterogeneity decreased in the MSC injection subgroup ($I^2$=59%) but increased slightly in the MSC surgical adjunct cohort ($I^2$=82%). Sub-analysis resulted in a SMD 0.33 (95% CI: -0.13-0.78, p=0.16) and 0.05 (95% CI: -0.92-1.03, p=0.91), respectively (**Figure 3**). The test for subgroup differences in SMD was not significant (p=0.62).

*Self-reported Physical Function*

Twenty-two studies reported functional outcome scores, with seven studies and eight data sets comparing functional improvement between MSC treatment (n = 161) and control (n = 164) cohorts. Self-reported physical function questionnaires included the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) functional score, International Knee Documentation Committee (IKDC) score, Lysholm scores, and Knee Injury and Osteoarthritis Outcome Score (KOOS). The mean follow-up time for these six studies was 20.0 ± 9.9 months (range, 12.0-38.8 months). Combining all seven studies, the meta-analysis resulted in a pooled SMD of 0.66 (95% CI, 0.31 — 1.02), significantly favoring MSC treatment groups (p<0.001) (**Figure 4**). This statistical value corresponds to a mean difference in pre-to-post score change of 11.4 (95% CI, -0.98 – 24.0) in the WOMAC functional outcome (0 – 100 points); 11.8 (95% CI, 5.7 – 17.6) in the IKDC score (0 – 100 points); 8.2 (95% CI, -0.2 – 16.5) in the Lysholm score (0 – 100 points); and 4.0 (95% CI, 0.8 – 7.3) in the KOOS Activities of Daily Living (ADL)

subscale. The estimate of heterogeneity among the six included studies was moderate ($I^2$ = 54%).

Similar to the sub-analysis performed for the VAS pain scale, stratification and sub-analysis of studies that administered MSC via injection only versus with a surgical adjunct was performed (**Figure 5**). The mean follow-up period was not significantly different between the subgroups (p=0.05). Within the MSC injection subgroup, functional benefits were non-significant (pooled SMD: 0.70, 95% CI: -0.06—1.47, p=0.07) and moderate heterogeneity ($I^2$ = 64%) was observed. In contrast, functional benefits among adjunct MSC with surgery cohorts significantly favored MSC (pooled SMD: 0.64, 95% CI: 0.31 – 1.02, p<0.001) without significant heterogeneity ($I^2$=22%). The test for subgroup differences in SMD was not significant (p=0.89).

*Structural Changes in Articular Cartilage*

Five studies reported changes in cartilage volume following MSC treatment.[3, 19, 29, 31, 46] Two studies with five data sets assessed improvement in cartilage volume between MSC treatment (n = 104) and controls (n = 108).[29, 31] Mean follow-up in these studies was 9.0 ± 4.2 months. Meta-analysis yielded a pooled SMD of 0.84 (95% CI, 0.55 — 1.12) that significantly favored MSC treatment (p<0.001) (**Figure 6**). This statistical value corresponds to a mean difference of 2,940 $mm^3$ (95% CI, 1,925 — 3,920 $mm^3$) and 1,764 $mm^3$ (95% CI, 1,155 — 2,352 $mm^3$) in total and femoral cartilage volume, respectively.

Regarding cartilage quality, three studies investigated improvement between MSC treatment (n=57) and controls (n=58).[15, 16, 53] Mean follow-up for these studies was 11.0 ± 0.6 months. Meta-analysis resulted in a small effect size of 0.37 (95%, -0.03 – 0.77) that favored MSC treatment, but was not statistically significant (p=0.07) (**Figure 7**). Estimates of heterogeneity among the included studies was low ($I^2$ = 9%).

## DISCUSSION

The main findings of the current study are: (1) the majority of studies reported improvements in patient-reported pain and physical function following mesenchymal stem cell (MSC) interventions; however, meta-analyses found that only self-reported physical function significantly improved relative from controls, (2) MSC treatment results in significant improvement in cartilage volume, but not cartilage quality, relative to controls and (3) there is limited evidence in the current literature to support MSC-induced cartilage regeneration.

*Patient-reported Outcomes*

There was significant variability in patient-reported pain improvement between MSC and control groups. Consequently, meta-analysis failed to demonstrate superior improvement in postoperative pain relative to controls. A previous systematic review concluded that MSC treatment resulted in significantly improved VAS pain scores at 24-months.[58] Another meta-analysis reported pain improvement at 24 months that significantly favored MSC treatment.[8] However, these studies reported improvements in pain relative to baseline, rather than differential improvement in the MSC treatment group versus matched controls. Because the analyses in the current study included matched-control groups, the conclusions potentially have greater validity and applicability, despite their significant variability.

One potential factor implicated in the efficacy of MSCs for pain mitigation and analgesia is dose-response. Prior studies have demonstrated differences in pain response depending on MSC concentration and dose. Gupta et al. reported improved outcomes in pain measurement scores in the low-dose group (25 million cells), but no improvement in the higher dose groups.[15] They proposed that a dose of 25 million cells may be optimal with the 2 mL of hyaluronic acid used as supportive matrix. Secondly, they proposed that the 25-million-cell dose group may be optimal for the limited intra-articular space in the knee joint. Gupta et al. also postulated that MSC doses greater than 25 million cells may cause cell aggregation due to high cell

concentration or insufficient knee joint space, consequently causing cell death. Additionally, higher doses of MSCs may potentially cause MSCs behave as M1-type cells with a pro-inflammatory response, compared to lower MSC doses that may be the ideal cell concentrations giving rise to an M2-type MSC with an immunosuppressive/anti-inflammatory response.[44] Finally, a limitation highlighted in Gupta et al. was the unblinding of patients after six months follow-up, which could have influenced subjective patient-reported outcome measures evaluating pain.[15]

In contrast, the pooled results of patient-reported physical function showed significant improvement with MSCs. There are a number of potential explanations for this discrepancy and the lack of significant pain improvement, despite functional response. There is considerable variability in the included study protocols that could potentially contribute to these results. For example, patient factors including OA grade, lesion size, alignment, and comorbid conditions could affect patient-reported responses on pain and physical function. Treatment factors (i.e. MSC type, source site), administration technique, concomitant procedures (i.e. HTO or microfracture), and concomitant injections (i.e. hyaluronic acid, PRP) all contribute to the possible explanations for discrepant patient-reported pain and functional outcomes. While this is difficult to standardize, future studies with uniform protocols should be repeated in order to establish the best method of administration of MSCs. Alongside uniform protocols, standardization of MSC preparation should be implemented in future studies. These study protocols emphasize the incredibly diverse patient populations and methodologies included in these studies, rendering it difficult to draw direct conclusions despite the high quality of evidence in each included study.

Due to inherent difficulties in interpretation of SMD in the clinical context, mean differences in change (pre-to-post delta) for functional outcome scores were calculated to determine if these values represented a clinically significant difference. The meta-analysis yielded a mean difference in change between MSC and controls of 11.4, 11.8, 8.2, and 4.0

points for WOMAC functional outcome, IKDC, Lysholm, and KOOS ADL, respectively. These scores exceeded established values of minimal clinically important difference (MCID) for WOMAC physical function (MCID=8.1 – 9.1)[14, 49] and IKDC (MCID=6.3 – 10.6),[13, 14] but not KOOS ADL (MCID=11.0)[13] at the 6-month postoperative time point. No studies examining knee osteoarthritis or cartilage procedures have established MCID for the Lysholm score. These results suggest that treatment with MSC may confer functional benefits that are clinically significant and perceptible to patients; however, high risk for bias and a small number of studies qualifying for meta-analysis render this conclusion speculative, necessitating future corroborating research.

To address the inclusion of studies that implemented concomitant surgical procedures or surgically administered MSCs, two sub-analyses stratifying studies based on whether MSCs were administered via injection versus with a surgical adjunct were performed. In terms of patient-reported pain, neither subgroup significantly favored MSC. The test for subgroup differences in SMD was also not significant, indicating that one method of MSC implementation is not superior to the other. Regarding patient-reported physical function, functional benefits were non-significant within the MSC injection subgroup. In contrast, functional benefits among adjunct MSC with surgery cohorts significantly favored MSC based on sub-analysis. However, because the test for subgroup differences in SMD was not significant, there is insufficient evidence to broadly conclude that MSCs with surgical adjunct is superior to the MSC injection subgroup. These results must be interpreted with extreme caution as there was there was substantial heterogeneity in the protocols implemented to control and treatment groups. For example, some studies administered MSC with PRP,[24-26] while others administered MSCs at the time of surgery (HTO).[23, 55] Furthermore, there was heterogeneity of concomitant procedures and adjunctive treatment. Koh et al. divided enrolled patients into two groups: the control group would undergo high tibial osteotomy (HTO) with platelet-rich plasma (PRP) injection and the MSC treatment group would undergo HTO with PRP injection and MSC therapy.[26] The

388 presence of heterogeneity in these sub-analyses further illustrates the notion that there are a
389 variety of confounding variables proving difficult to isolate, thus necessitating the creation of
390 standardized protocols for MSC administration.
391
392 *Structural Changes in Articular Cartilage*
393 The role of MSCs in cartilage restoration and regeneration is highly controversial. Based
394 on our analysis, there remains limited evidence to support the effect of MSC treatment on
395 cartilage restoration relative to control. This meta-analysis aimed to exclusively include studies
396 reporting differential changes in cartilage quantity and quality between treatment and control
397 groups.
398 Based on pooled studies investigating structural changes in cartilage volume, there was
399 a significant increase in cartilage volume after MSC treatment compared to controls. This finding
400 contradicts the results of a previous study that found no significant improvement in cartilage
401 volume with MSC treatment.[18] Although this finding is promising and may suggest that MSC
402 treatment may play a potential role in cartilage regeneration, several key questions remain. The
403 proposed mechanism for this change is not clear, as this could be attributed to a direct
404 progenitor effect or more likely a pleiotropic effect of MSCs. It is also not known if this effect on
405 cartilage volume is sustained beyond one year. Overall, this conclusion is limited by the short-
406 term follow up of the included studies. Future studies should be aimed at investigating MSC
407 effect on cartilage volume at further timepoints beyond one year.
408 Regarding cartilage quality, there was no significant improvement when comparing MSC
409 treatment and controls from baseline to final follow-up. However, when individually assessing
410 the three studies eligible for meta-analysis, two studies reported improvement between MSC
411 treatment and control.[16, 53] Hashimoto et al. reported a significantly higher mean MOCART score
412 in the MSC + microfracture group than in the control group (microfracture alone).[16] Additionally,
413 Vega et al. found that quantification of cartilage quality by T2 relaxation measurements showed

414 a significant decrease in poor cartilage areas, with cartilage quality improvements in MSC-
415 treated patients.[53] In contrast, Gupta et al. detected no significant difference in cartilage signal
416 and morphology on MRI between MSC and controls.[15] Gupta et al. proposed multiple
417 explanations for this finding. They postulated that the type of MSCs used may be different from
418 one study to another, or that there were a limited number of patients included in the study's MRI
419 analysis.[15] Despite the lack of statistical significance, the pooled standardized mean difference
420 (SMD) was small in size (0.37). These results are promising; however, it is still difficult to make
421 generalizing conclusions about MSC effect on cartilage quality due to the paucity and variability
422 of studies comparing improvement in cartilage quality relative to controls. The lack of studies
423 containing a matched-cohort group highlights the necessity for future comparative studies with
424 appropriate controls. More specifically, future studies conducted should compare MSC effect on
425 cartilage regeneration between treatment and control groups.

426 Many included studies utilized the MOCART classification, which is one of the most
427 frequently used MR scores for postoperative cartilage repair tissue evaluation.[32] While this
428 validated scoring tool offers many benefits, it does not allow for baseline comparison of cartilage
429 quality. Future studies should implement knee MR scores that enable baseline measurements
430 to allow for comprehensive comparison, such as the MRI Osteoarthritis Knee Score (MOAKS).[24]
431 This knee MR score provides a semiquantitative analysis of knee OA,[43] and includes evaluation
432 of key variables such as area of cartilage loss and percentage of full-thickness cartilage loss at
433 preoperative and final follow up time points.[24] Widespread implementation of MOAKS in
434 analysis of MSC treatment would permit greater data collection of MSC effects on cartilage
435 regeneration.

436

437 *Cost-Analysis*

438 While cell therapies have been more frequently utilized in orthopedic surgery compared
439 to other specialties, there are still considerable barriers to commercial implementation.

According to Davies et al., the most concerning barriers to adoption include cost-effectiveness and efficacy, followed by regulation, reimbursement, and safety.[10] Specifically, orthopedic surgeons surveyed identified “clinical trial methodologies” as a large barrier to implementation. Clinical trial methodologies were defined as the quality and rigor of clinical trial designs implemented. The growing popularity and desire for implementation of stem-cell therapies must be equally balanced with focused debate regarding cost-effectiveness and strong evidence-based justification for use in orthopedic patients.

Risk of Bias

The Downs and Black scale is a well-established checklist that allows for assessment of a paper’s methodological strengths and weaknesses. After completing Downs and Black Scores for all included studies, over half of the studies received a categorical grade of “poor” or “fair” (68%). Consequently, while MSC treatment resulted in significant improvement in cartilage volume, but not cartilage quality (relative to controls), this must be interpreted judiciously in the context of high risk of bias. Future studies need to be conducted not only with high quality evidence, but with strong internal validity in order to help address the levels of bias seen in the included studies.

*Limitations*

The results of the current study should be interpreted in the context of a few limitations. First, there were a limited number of studies that qualified for our meta-analyses, as the studies were required to have matched-control group for comparison with the MSC-treated arm. There is also significant variability in the source, preparation, concentration of currently utilized MSC products. These differences between studies can confound comparisons and limit conclusions

that can be drawn. Additionally, it is not clear how MSCs were typed, prepared, and processed in each study.

## CONCLUSION

In conclusion, the pooled standard mean difference from meta-analyses showed statistically significant effects of MSC on self-reported physical function but not self-reported pain. MSCs provided functional benefit only in patients who underwent concomitant surgery. However, this must be interpreted with caution as there was substantial variability in MSC composition and mode of delivery. MSC treatment provided significant improvement in cartilage volume, but not cartilage quality. Preliminary data regarding therapeutic properties of MSC treatment suggest significant heterogeneity in the current literature and risk of bias is not negligible.

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Figure Legends

**Figure 1**. PRISMA diagram outlining steps included in the systematic review of queried articles.

**Figure 2.** Forest plot reporting pre- to post-treatment differences comparing control and MSC treatment groups for self-reported knee pain, including the summary estimate (center of diamond) and 95% confidence interval (CI, width of diamond) at furthest follow-up. Means and standard deviations (SD) are reported as numeric values on the visual analog scale (VAS).

IV: inverse variance

**Figure 3.** Forest plot reporting pre- to post-treatment differences comparing studies that administered MSC via injection only versus MSCs administration in conjunction with a surgical adjunct, including the summary estimate (center of diamond) and 95% confidence interval (CI, width of diamond) at furthest follow-up. Means and standard deviations (SD) are reported as numeric values on the visual analog scale (VAS).

IV: inverse variance

**Figure 4.** Forest plot reporting pre- to post-treatment changes comparing control and MSC treatment groups for self-reported physical function, including summary estimates (center of diamond) and 95% confidence intervals (CI, width of diamond) at furthest follow-up. Means and standard deviations (SD) are reported according to each respective patient-reported outcome (PRO) scoring scale.

IV: inverse variance; WOMAC: Western Ontario and McMaster Universities Index; IKDC: International Knee Documentation Committee; KOOS: Knee Injury and Osteoarthritis Outcome Score

**Figure 5.** Forest plot reporting pre- to post-treatment differences comparing studies that administered MSC via injection only versus with a surgical adjunct for self-reported physical function, including summary estimates (center of diamond) and 95% confidence interval (CI, width of diamond) at furthest follow-up. Means and standard deviations (SD) are reported according to each respective patient-reported outcome (PRO) scoring scale.

IV: inverse variance; WOMAC: Western Ontario and McMaster Universities Index; KOOS: Knee Injury and Osteoarthritis Outcome Score

**Figure 6.** Forest plot reporting pre- to post-treatment changes comparing control and MSC treatment groups for cartilage volume, including a summary estimate (center of diamond) and 95% confidence interval (CI, width of diamond) at final follow-up. Means and standard deviations (SD) are reported in millimeters cubed ($mm^3$).

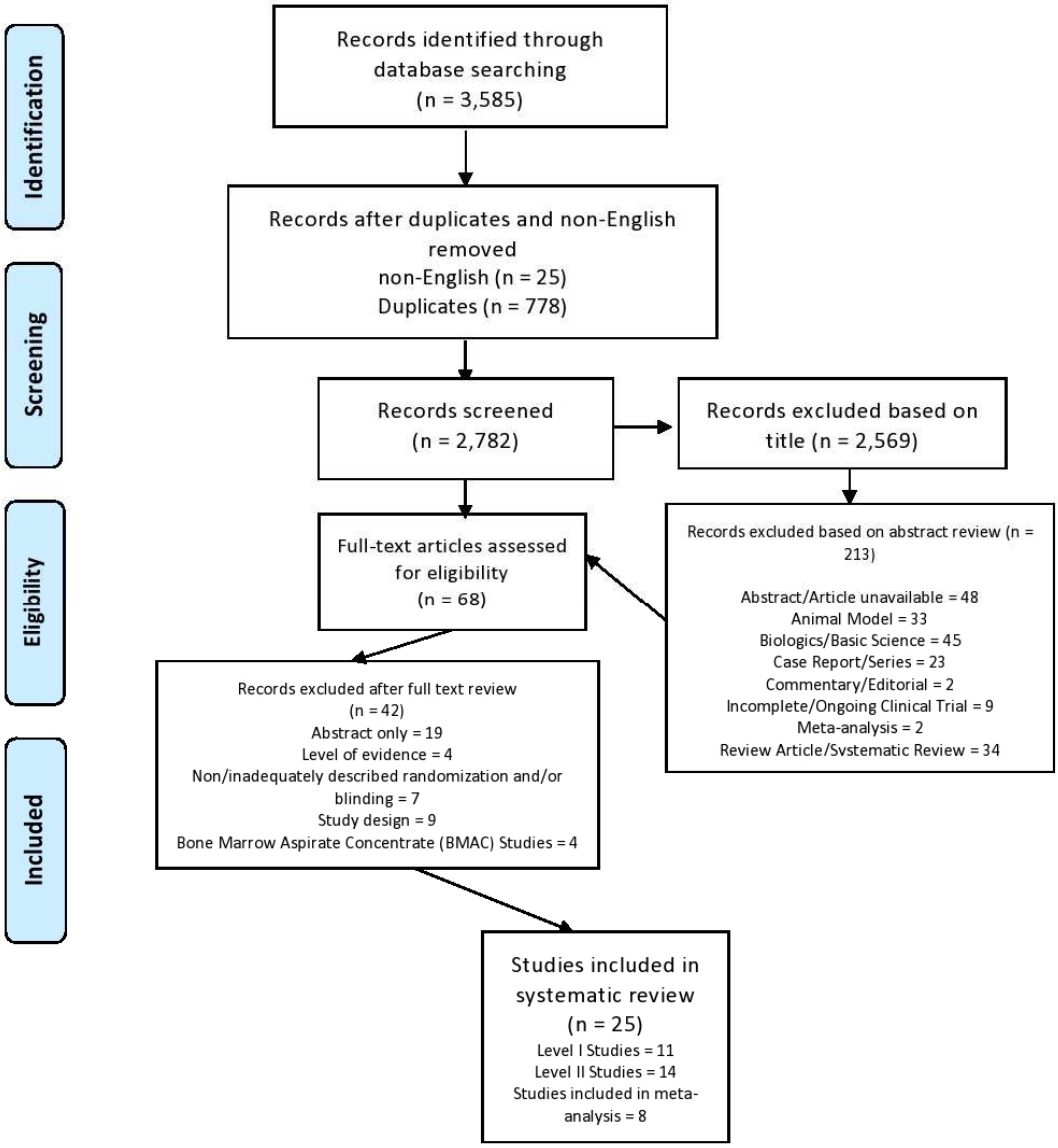
IV: inverse variance; F: femoral; T: total; R: right leg; L: left leg

**Figure 7.** Forest plot reporting pre- to post-treatment changes comparing control and MSC treatment groups for cartilage quality, including summary estimates (center of diamond) and 95% confidence interval (CI, width of diamond) at final follow-up. Means and standard deviations (SD) are reported according to each respective scoring scale.

IV: inverse variance; MOCART: magnetic resonance observation of cartilage repair tissue; WORMS: whole-organ magnetic resonance imaging score

723 Figure 1.

| Author | | K-L Inclusion | Study Group | Donor | Control Group |
|---|---|---|---|---|---|




724

| | | | Knees (n) | Mean age (years) | M/F | Treatment (dose) | | Knees (n) | Mean age (years) | M/F | Treatmen (dose) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Akgun[2] | I (RCT) | Grade III-IV | 14 | 32.3 ± 7.9 | 4/3 | matrix induced MSC | AUTO | 7 | 32.7 ± 10.4 | 4/3 | m-ACI |
| Gupta[15] | I (RCT) | Grade I-III | 40* | 56.1 ± 7.7* | 12/28* | BD-MSC | ALLO | 20* | 55.8 ± 6.8* | 3/17* | ------ |
| Goncars[12] | I (RCT) | Grade II-III | 28 | 53.44 | 15/13 | ----- | AUTO | 31 | 58.55 | 10/21 | ------ |
| Hashimoto[16] | I (RCT) | Grade I-III | 7 | 42.6 | 3/4 | Cell-t group | AUTO | 4 | 46.3 | 4/0 | Placebo |
| Koh[26] | I (RCT) | Grade I-II | 21 | 54.2 ± 2.9 | 5/16 | MSC-PRP | AUTO | 23 | 52.3 ± 4.9 | 6/17 | PRP only |
| Koh[27] | I (RCT) | Grade I-II | 40 | ------ | 14/26 | MFX + ADSCs | AUTO | 40 | ----- | 16/24 | MFX only |
| Kuah[28] | I (RCT) | Grade I-III | 16 | 52.6 | 8/2 | ADMSC (3.9 million) | ALLO | 4 | 55 ± 10.42 | 1/3 | Placebo |
| Lee[29] | I (RCT) | Grade II-IV | 12 | 62.2 ± 6.5 | 3/9 | ADMSC ($1.0x10^8$) | ALLO | 12 | 63.2 ± 4.2 | 3/9 | Saline |
| Lu[31] | I (RCT) | Grade I-IV | 26 | 55.03 | 3/23 | *Re-Join* MPC treatment (AD with cell suspension) | AUTO | 26 | 59.64 | 3/23 | HA |
| Turajane[50] | I (RCT) | Grade II-III | 40** | 55.15** | 13/27** | AAPBSC + GFA + HA + MSC | AUTO | 20 | 54.7 | 6/14 | HA alone |
| Wong[55] | I (RCT) | ------ | 28 | 53 | 13/15 | HTO + BD-MSC ($1.5 \times 10^7$) | AUTO | 28 | 49 | 14/14 | HTO |
| Vega[53] | I (RCT) | Grade II-IV | 15 | 57 | 13/17 | BM-MSC ($40x10^6$) | ALLO | 15 | ----- | ------- | HA |
| Wakitani[54] | I (RCT) | ----- | 12 | ---- | ----- | BM-MSC | AUTO | 12 | ----- | ----- | Cell-free controls |

Table 1a. Summary of Included Level I Studies.

*Study Group: Cohort 1: (low dose)-N=10, 58.1(8.2), 3/7 (mid-dose)-N=10, 57.3(9.5), 2/8Cohort 2: (high dose) N= 10, 55.0(6.7) 2/8 (very high)-N=10, 54.0(6.7) 5/5; Control Group: Cohort 1: n=10, 54.9(8.3), 0/10; Cohort 2: n=10, 56.7(5.2) 3/7

**Group 1: n=20, 54.9, 10/10, Group 2: n=20, 55.4 3/17

K-L: Kellegren-Lawrence, M/F: Male/Female, MRI: Magnetic resonance imaging, m-ACI: matric-induced autologous chondrocyte implantation, VAS: Visual Analog Scale, KOOS: Knee Injury and Osteoarthritis Outcome Score, BD-MSC: Bone marrow-derived mesenchymal stem cells; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index, WORMS: Whole Organ Magnetic Resonance Imaging Score, AMIC: Autologous matrix-induced chondrogenesis, BMAC: Bone marrow aspirate concentrate, KSS: Knee society score, OAOS: osteo-arthritis outcome score; MOCART: Magnetic resonance of cartilage repair tissue, MSC-PRP: mesenchymal stem cells-platelet rich plasma, MFX: microfracture, ADSC: adipose-derived stem cells, MPC: Mesenchymal progenitor cells, HA: hyaluronic acid, SF-36: 36 item short-form questionnaire, ICOAP: Intermittent and constant osteoarthritis pain questionnaire, AAPBSC: Autologous activated peripheral blood stem cells, GFA: growth factor addition, HTO: High tibial osteotomy, QOL: Quality of life, ICRS: International Cartilage Regeneration and Joint Preservation Society, HSS: Hospital for Special Surgery score, RCT: Randomized controlled trials

Table 1b. Summary of Included Level II Studies.

| Author | Level of Evidence | K-L Inclusion | Study Group | | | | Donor | Control Group | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Knees (n) | Mean age (years) | M/F | Treatment (dose) | | Knees (n) | Mean age (years) | M/F | Treatment (dose) |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Al-Najar[3] | II (NRCS) | Grade II/III | 13 | 50 | 6/7 | 1 x $10^6$ | AUTO | ---- | ----- | ---- | ----- |
| Chahal[4] | II (NRCS) | Grade III-IV | 12 | 40-65 (range) | ----- | BM-MSC (1 x $10^6$, 10 x $10^6$, 50 x $10^6$) | AUTO | ---- | ----- | ---- | ----- |
| Jo[20] | II (NRCS) | Grade lII-IV | 18* | 62.3 ± 7.1* | 3/15* | AD-MSC* | AUTO | ---- | ----- | ---- | ----- |
| Kim[22] | II (NRCS) | Grade I-II | 17 | 57.7 | 8/9 | ADMSC w/ scaffold | AUTO | 37 | 57.5 | 14/23 | MSC no scaffold |
| Kim[23] | II (NRCS) | Grade III-IV | 50 | 59.2 | 16/34 | HTO + ADMSC | AUTO | 50 | 58.3 | 16/34 | HTO |
| Pers[39] | II (NRCS) | Grade III-IV | 18** | 64.7 ± 4.8 | 8/10** | AD-SVF** | AUTO | ---- | ----- | ---- | ----- |
| Park[38] | II (NRCS) | Grade III | 7 | 58.7 ± 15.4 | 2/5 | Umbilical blood-MSC | ALLO | ---- | ----- | ---- | ----- |
| Spasovski[47] | II (NRCS) | ----- | 9 | ----- | ----- | AD-MSC (0.5-1 x $10^7$) | AUTO | ---- | ----- | ---- | ----- |
| Song[46] | II (NRCS) | Grade 0-IV | 18 | ----- | ----- | AD-MSC (1 x $10^7$, 2 x $10^7$, 5 x $10^7$) | AUTO | ---- | ----- | ---- | ----- |
| Kim[21] | II (SAPS) | Grade I-II | 24 | 57.9 | 11/9 | AD-MSC | AUTO | ---- | ----- | ---- | ----- |
| Koh[25] | II (SAPS) | Grade I-III | 25 | 54.2 ± 9.3 | 8/17 | MSC + PRP + debridement (1.89 x $10^6$) | AUTO | 25 | 54.4 ± 11.3 | 8/17 | PRP + arthroscopy |
| Kim[24] | II (SAPS) | Grade I-II | 40 | 59.2 ± 3.3 | 14/26 | MSC + PRP or fibrin scaffold | AUTO | ---- | ----- | ---- | ----- |

*Study Group: n=3, 63(8.6), 1/2, low dose; n=3, 63(6.6), 0/3, mid dose; n=12, 61(6.2) 2/10, high dose; AD-MSC (Low dose $1.0 \times 10^7$ mid dose $5.0 \times 10^7$ high dose $1.0 \times 10^8$)

**Study Group: n=6, 63.2(4.1), 3/3, low dose; n=6, 65.6 (8.1) 3/3, mid dose; n=6, 65.2(2.3) 2/4, high dose; AD-SVF injection (low dose: 2 × 10^6, mid dose: 10 × 10^6, high dose: 50 × 10^6 cells)

K-L: Kellgren-Lawrence, M/F: Male/Female, NRCS: Non-randomized comparative studies, SAPS: Single-arm prospective studies MRI: Magnetic resonance imaging, m-ACI: matric-induced autologous chondrocyte implantation, VAS: Visual Analog Scale, KOOS: Knee Injury and Osteoarthritis Outcome Score, BD-MSC: Bone marrow-derived mesenchymal stem cells; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index, WORMS: Whole Organ Magnetic Resonance Imaging Score, AMIC: Autologous matrix-induced chondrogenesis, BMAC: Bone marrow aspirate concentrate, KSS: Knee society score, OAOS: osteo-arthritis outcome score; MOCART: Magnetic resonance observation of cartilage repair tissue, MSC-PRP: mesenchymal stem cells-platelet rich plasma, MFX: microfracture, ADSC: adipose-derived stem cells, HA: hyaluronic acid, SF-36: 36 item short-form questionnaire, ICOAP: Intermittent and constant osteoarthritis pain questionnaire, AAPBSC: Autologous activated peripheral blood stem cells, GFA: growth factor addition, HTO: High tibial osteotomy, QOL: Quality of life, ICRS: International Cartilage Regeneration and Joint Preservation Society, AD-SVF: Adipose derived stromal vascular fraction, HSS: Hospital for Special Surgery score, MOAKS: MRI osteoarthritis knee score

Table 2. Cell Therapy Descriptions for all included studies.

| Study | Source Site | Collection Technique | Initial Volume | Source | Cell Type | No. of Cells (x$10^6$) | Injection Site/Technique | Delivery Solution | Qualitativ markers |
|---|---|---|---|---|---|---|---|---|---|

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Akgun[2] | Synovia | From femoral condyles | 5 mm cartilage chip | Auto | MSC | ~8 | NR | Implantation via mini-arthrotomy | CD105+, CD14-, CI |
| Gupta[15] | BMA | NR | In 15 mL PLASMA-LYTE A | Allo | BM-MSC | 200 | Lateral midpatellar | IMP injection followed by 2 mL HA | CD73+, C CD45-, CI |
| Goncars[12] | BMA | NR | 45 mL into heparin-treated syringes | Auto | BM-MNC | NR | NR | 5-10 mL saline injected + MNCs | CD34+, C |
| Hashimoto[16] | BMA | From PSIS | 30-40 mL | Auto | BM-MSC | NR | MFX of cartilage lesion | Suspended in 2.4 mL HA | CD44+, C |
| Koh[26] | Adipose | Tumescent liposuction | 120 mL for injection, 20 for lab analysis | Auto | MADNC | 48.3 | Medial, arthroscopic guidance | In 3 mL PRP after arthroscopy, before HTO | CD90+, C |
| Koh[27] | Adipose | Liposuction | NR | Auto | ADSC | NR | MFX 3-4 mm apart | SVF + MSC implanted into each well on cartilage lesion surface | CD90+, C |
| Kuah[28] | Adipose | NR | NR | Allo (1 donor) | AD-MSC | 3.9, 6.7 | NR | Intra-articular injection | NR |
| Lee[29] | Adipose | Tumescent Lipoaspiration | 20 mL adipose tissue | Auto | AD-MSC | 100 | US-guided intra-articular injection | MSCs in 3 mL of saline | CD31, CD |
| Lu[31] | Adipose | Liposuction | NR | Auto | AD-MPC | 50 | NR | ~2.5 mL ADMPC intra-articular injection | Profile of |
| Turajane[50] | Peripheral Blood | Leukapheresis and hG-CSF | 3 mL, with portion frozen for intra-articular injection | Auto | AA-PBSC | 1.0-1.3 | Arthroscopic debridement and drillings of 2 mm | 3 mL AAPBSC injected + 2 mL GFA concentrate from PRP + hG-CSF | CD34+. C |
| Wong[55] | BMA | NR | 49 mL (median) | Auto | CEAC | 14.6 | NR | 0.5-1 mL autologous serum + 2 mL HA | CD73+, C CD34-, CI |
| Vega[53] | BMA | Multiple repeated aspiration (2-4 mL BMA) under iliac spine | 80 mL | Allo | BM-MSC | 40 | Medial parapatellar | Suspended in Ringer lactate at $5x10^6$ cells/mL | Profile of for MSCs |
| Wakitani[54] | BMA | Both sides of iliac crest ~2 cm from ASIS | 10 mL embedded in 2 mL of acid soluble collagen | Auto | BM-MSC | 10 | Medial Parapatellar | Cell-gel composite put on abraded area of knee | NR |
| Al-Najar[3] | BMA | Multiple small aspirations from iliac crest | 35-40 mL | Auto | BM-MNC | 30.5 | Lateral tibiofemoral | BM-MSCs suspended in 5 mL NS | Profile of for MSCs |
| Chahal[4] | BMA | PSIS | 50 mL, with 25 mL collected for generating autologous serum | Auto | BM-MSC | 30 | NR | US-guided intra-articular injection | CD73, CD HLADR, |
| Jo[19] | Adipose | Liposuction | NR | Auto | AD-MSC | 10, 50 | Mesial portal of the knee | ADMSCs in 3 mL of saline injected | CD31, CD |
| Kim[22] | Adipose | Tumescent liposuction | 140 mL, with 120 mL used for injection and 20 mL for analysis | Auto | AD-MSC | 3.9 | Arthroscopic implantation | Articular cartilage lesion filled with MSCs (Group 1), Fibrin glue + thrombin/fibrinogen solution (Group 2) | CD90+, C |
| Kim[23] | Adipose | Tumescent liposuction | NR | Auto | AD-MSC | 4.26 | Medial, arthroscopic guidance | NR | CD90+, C |
| Pers[39] | Adipose | Liposuction | 10 g aliquots of adipose tissue | Auto | AASC | 0.20 | US-guided injection | 5 mL single intra-articular dose of ASCs | CD90+, C CD34- |
| Park[38] | Human umbilical cord blood | From umbilical veins at time of neonatal delivery | NR | Auto | hUCB-MSC | 5.0 | Holes made at cartilage defect site of femoral condyle | MSCs Implanted in drill holes of lesions | Profile of for MSCs |
| Spasovski[47] | Adipose | Small incision under local anesthesia | 5 mL | Auto | AD-MSC | 5-10 | NR | MSC loaded into 2 mL syringes and injected into affected joint | CD34, CD |
| Song[46] | Adipose | Liposuction | NR | Auto | ha-MSCs | 10, 20, 50 | Medial portal under US-guidance | 3 mL cell suspension into both knee joints | CD90+, C CD45-, HI |
| Kim[21] | Adipose | Liposuction | 140 cc, with 120 cc used for implantation and 20 cc for cell analysis | Auto | AD-MSC | 4.4 | Under arthroscopic guidance after arthroscopic fluid extracted | Cell-thrombin-fibrinogen suspension applied using probe, coated at cartilage lesion surface | CD14, CD |
| Koh[25] | Adipose | Adipose tissue harvest from skin at arthroscopic lateral portal | 9.2 g (6.9-11.2 g range) | Auto | MADNC | 1.89 | Lateral approach, upper pole of patella | In 3 mL PRP | NR |
| Kim[24] | Adipose | Tumescent liposuction | NR | Auto | ADMSC | 4.01 | Injection via arthroscopic guidance | MSCs + 3 mL PRP | CD90+, C |

CTP: Connective tissue progenitor, CFU: colony forming unit, MSC: mesenchymal stem cells, NR: Not recorded, BMA: Bone marrow aspirate, IMP: Investigational medicinal product, MNC: Mononuclear cells, MFX: Microfracture, HA: Hyaluronic acid, MADNC: Mixed adipose derived nucleated cells, US: ultrasound, HTO: High tibial osteotomy, ADSC: Adipose derived stem cells, SVF: Stromal vascular fraction, ADMSC: Adipose-derived mesenchymal stem cells, ADMPC: Adipose derived mesenchymal progenitor cells, hG-CSF: Granulocyte colony stimulating factor, AAPBSC: Autologous activated peripheral blood stem cells, GFA: Growth factor addition, PRP: platelet-rich plasma CEAC: ISCT: BMMSC: Bone marrow mesenchymal stem cells, PI: Propidium iodide, hUCB-MSC: Human umbilical cord blood-derived mesenchymal stem cells, ha-MSC: human adipose-derived mesenchymal stem cells

Figure 2.

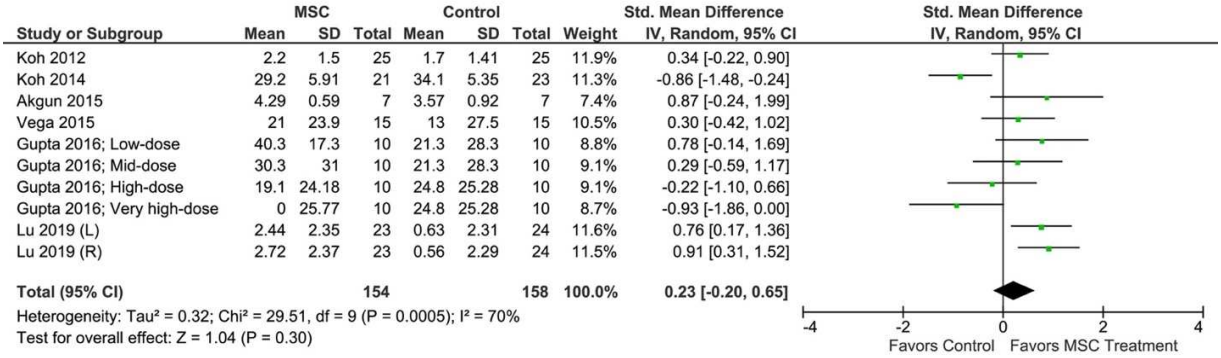



Figure 3.

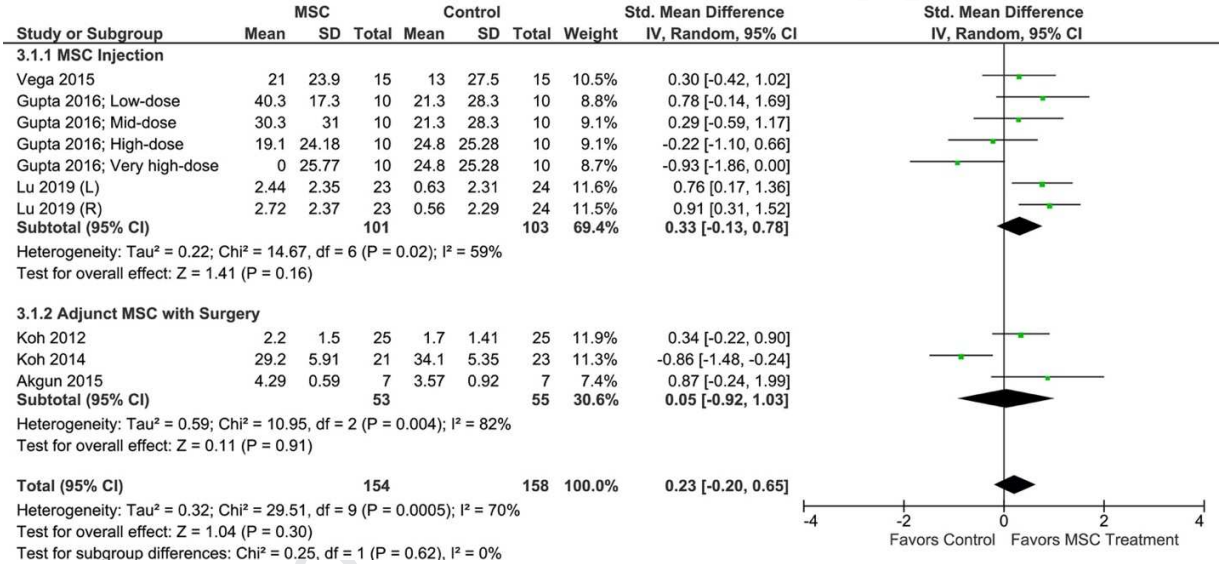



Figure 4.

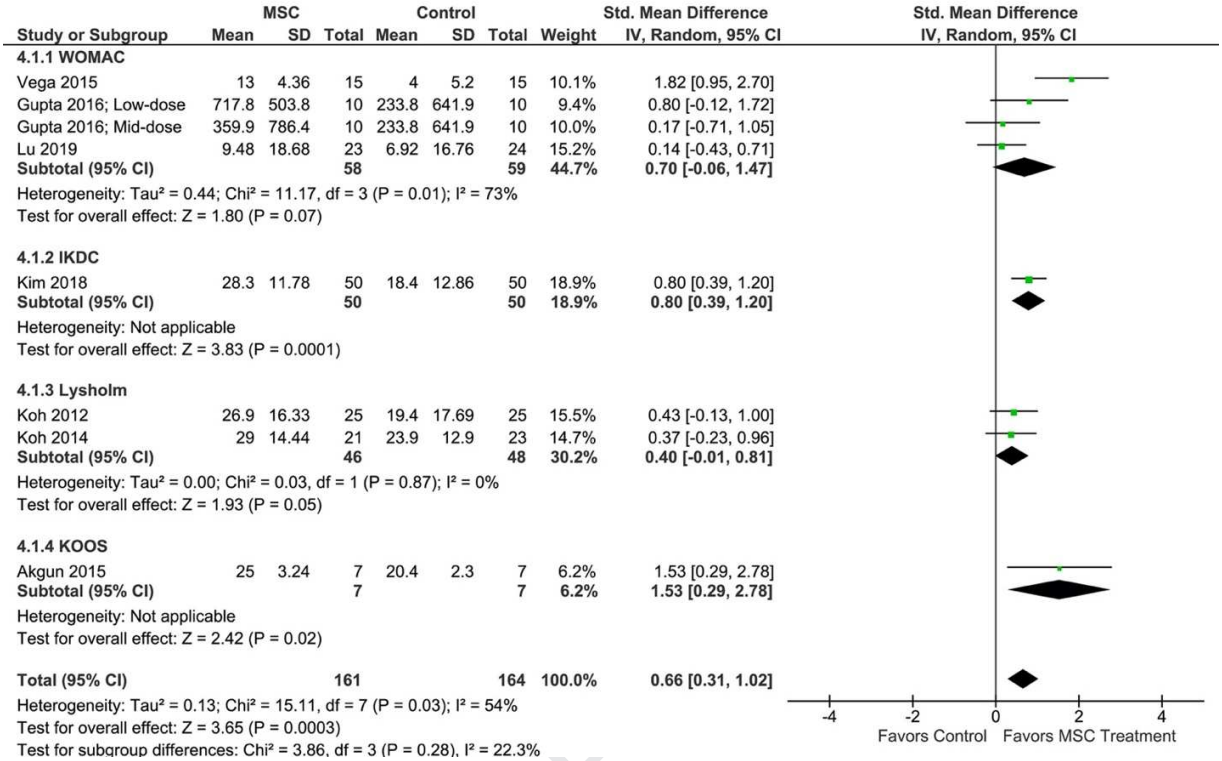



Figure 5.

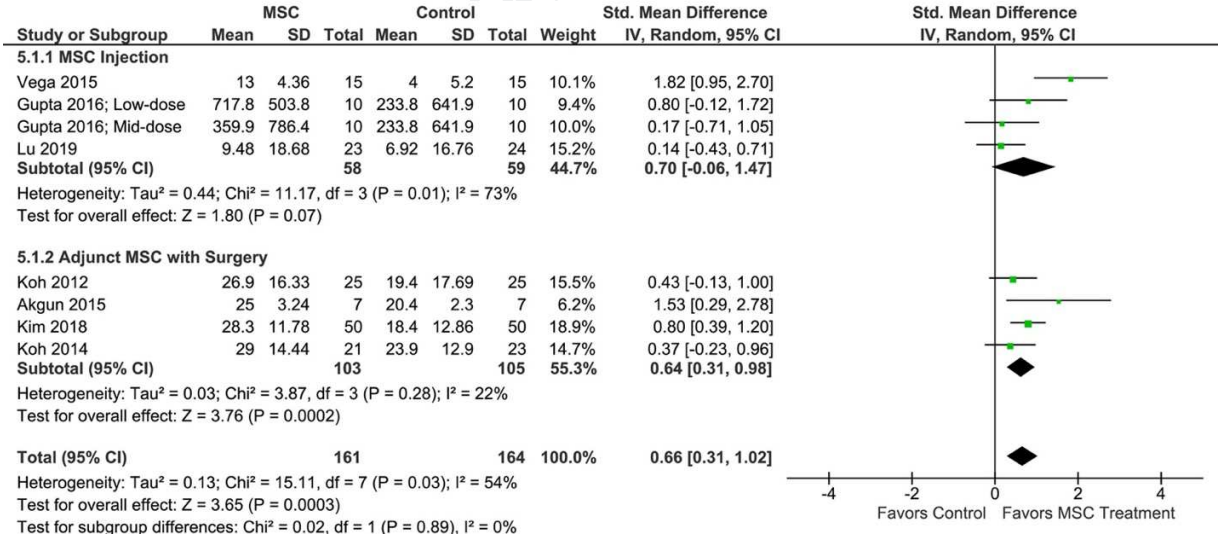



Figure 6.

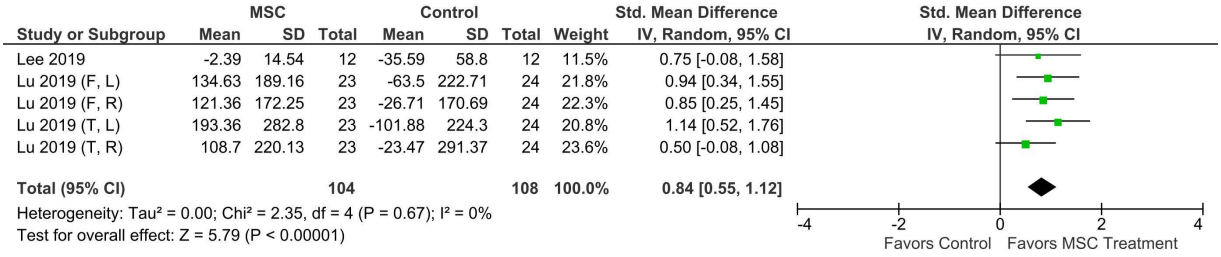
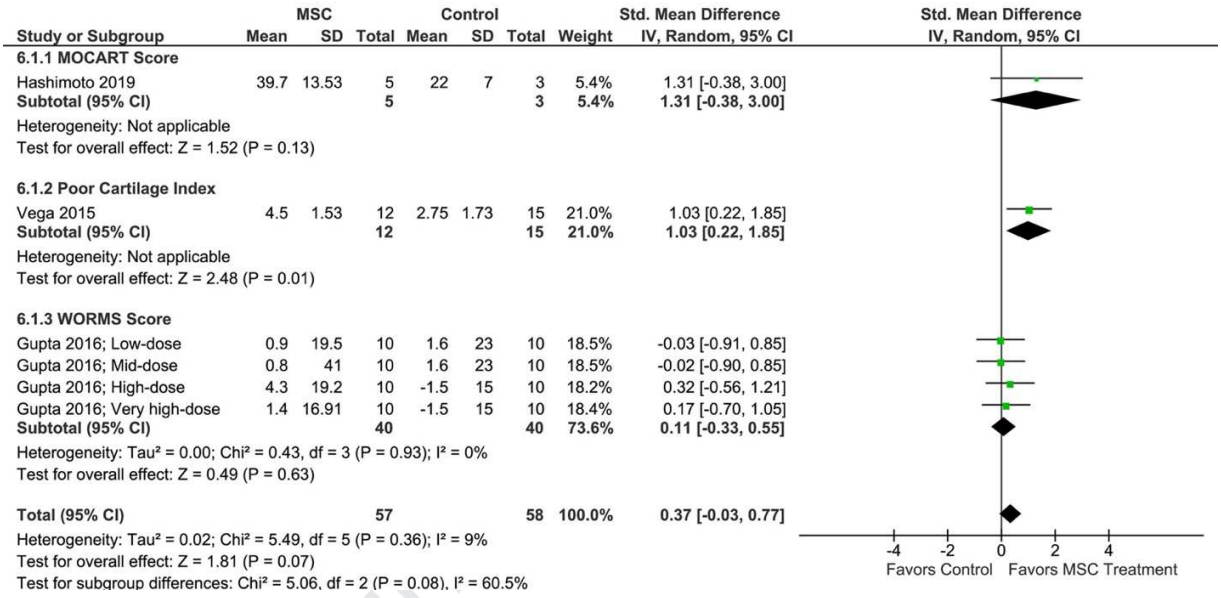

MSC
Control
Std. Mean Difference
Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
Lee 2019 -2.39 14.54 12 -35.59 58.8 12 11.5% 0.75 [-0.08, 1.58]
Lu 2019 (F, L) 134.63 189.16 23 -63.5 222.71 24 21.8% 0.94 [0.34, 1.55]
Lu 2019 (F, R) 121.36 172.25 23 -26.71 170.69 24 22.3% 0.85 [0.25, 1.45]
Lu 2019 (T, L) 193.36 282.8 23 -101.88 224.3 24 20.8% 1.14 [0.52, 1.76]
Lu 2019 (T, R) 108.7 220.13 23 -23.47 291.37 24 23.6% 0.50 [-0.08, 1.08]
Total (95% CI) 104 108 100.0% 0.84 [0.55, 1.12]
Heterogeneity: Tau² = 0.00; Chi² = 2.35, df = 4 (P = 0.67); I² = 0%
Test for overall effect: Z = 5.79 (P < 0.00001)
-4 -2 0 2 4
Favors Control Favors MSC Treatment

Figure 7.


MSC
Control
Std. Mean Difference
Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
6.1.1 MOCART Score
Hashimoto 2019 39.7 13.53 5 22 7 3 5.4% 1.31 [-0.38, 3.00]
Subtotal (95% CI) 5 3 5.4% 1.31 [-0.38, 3.00]
Heterogeneity: Not applicable
Test for overall effect: Z = 1.52 (P = 0.13)
6.1.2 Poor Cartilage Index
Vega 2015 4.5 1.53 12 2.75 1.73 15 21.0% 1.03 [0.22, 1.85]
Subtotal (95% CI) 12 15 21.0% 1.03 [0.22, 1.85]
Heterogeneity: Not applicable
Test for overall effect: Z = 2.48 (P = 0.01)
6.1.3 WORMS Score
Gupta 2016; Low-dose 0.9 19.5 10 1.6 23 10 18.5% -0.03 [-0.91, 0.85]
Gupta 2016; Mid-dose 0.8 41 10 1.6 23 10 18.5% -0.02 [-0.90, 0.85]
Gupta 2016; High-dose 4.3 19.2 10 -1.5 15 10 18.2% 0.32 [-0.56, 1.21]
Gupta 2016; Very high-dose 1.4 16.91 10 -1.5 15 10 18.4% 0.17 [-0.70, 1.05]
Subtotal (95% CI) 40 40 73.6% 0.11 [-0.33, 0.55]
Heterogeneity: Tau² = 0.00; Chi² = 0.43, df = 3 (P = 0.93); I² = 0%
Test for overall effect: Z = 0.49 (P = 0.63)
Total (95% CI) 57 58 100.0% 0.37 [-0.03, 0.77]
Heterogeneity: Tau² = 0.02; Chi² = 5.49, df = 5 (P = 0.36); I² = 9%
Test for overall effect: Z = 1.81 (P = 0.07)
Test for subgroup differences: Chi² = 5.06, df = 2 (P = 0.08), I² = 60.5%
-4 -2 0 2 4
Favors Control Favors MSC Treatment