



Clinical therapeutic efficacy of mesenchymal stem cells derived from adipose or bone marrow for knee osteoarthritis: a meta-analysis of randomized controlled trials

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Aim: This meta-analysis, only including randomized controlled trials (RCTs), was conducted to assess separately and compare the therapeutic efficacy of adipose-derived mesenchymal stem cells (ADMSCs) and bone marrow-derived mesenchymal stem cells (BMSCs) for knee osteoarthritis (OA) at the same follow-up time. **Methods:** Potential relevant researches were identified from PubMed, Web of Science, Embase, Cochrane Library and clinicaltrials.gov. The data, from clinical trials concentrating on knee OA treated with ADMSCs or BMSCs, were extracted and pooled for meta-analysis to compare the clinical outcomes of patients with knee OA in visual analog scale (VAS), Western Ontario McMaster Universities Osteoarthritis Index (WOMAC), Lysholm knee scale (Lysholm) and Tegner activity scale (Tegner). **Results:** Nine randomized controlled trials including a total of 377 patients met the inclusion criteria. This meta-analysis obtained the following results. First, the improvement of VAS scores was statistically significant after BMSCs treatment at 6-, 12- and 24-month follow-up compared with control groups ($p < 0.01$). In contrast, the improvement of WOMAC scores was of no statistical significance, but showed a positive trend with the prolongation of the follow-up time (6 months: mean difference [MD] = 6.51; 95% CI: -2.38 to 15.40; $p = 0.15$; 12 months: MD = -6.81; 95% CI: -13.94 to 0.33; $p = 0.06$). Lysholm scores presented a similar pattern (12 months: MD = 1.93; 95% CI: -11.52 to 15.38; $p = 0.78$; 24 months: MD = 8.94; 95% CI: 1.45 to 16.43; $p = 0.02$). Second, VAS and WOMAC scores of patients after ADMSCs treatment were significantly improved at any follow-up time ($p \leq 0.05$). The improvement of Lysholm scores was of no statistical significance compared with control groups, although treatment outcome at 12-month follow-up was better than that at 24-month follow-up, which was debatable because only data of one clinical trial were pooled in the analysis (12 months: MD = 7.50; 95% CI: -1.94 to 16.94; $p = 0.12$; 24 months: MD = 5.10; 95% CI: -3.02 to 13.22; $p = 0.22$). Finally, by comparing the statistical results of VAS and WOMAC scores, it could be concluded that the therapeutic effect of ADMSCs on knee OA was more effective than that of BMSCs. **Conclusion:** This meta-analysis showed that regeneration with BMSCs or ADMSCs had a great application potential in the treatment of patients with knee OA, and ADMSCs tended to be superior to BMSCs according to the limited clinical evidences available.

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Keywords: adipose-derived mesenchymal stem cells • bone marrow-derived mesenchymal stem cells • cartilage regeneration • knee osteoarthritis • meta-analysis

Knee osteoarthritis (OA) is the most common chronic degenerative joint disease, accompanied by pain, stiffness, swelling and functional disability, affecting the patients' quality of life to a severe extent [1]. The typical pathological characteristics are cartilage damage, synovial inflammation, osteophytes formation, ligaments tear and sub-chondral bone sclerosis [2–4]. The prevalence of knee OA increases with age, which climbs up to 33.6% for the elder over 65

years old [5,6]. In addition, knee OA is more common in women than men especially for symptomatic OA [4]. With the population of ageing and the burst of obesity, it is predicted that the prevalence of knee OA in people over 45 years will gradually increase from 13.8 to 15.7% by 2032 and that knee OA will probably become the fourth leading cause of disability by 2020 [4]. When it comes to global disease burden, knee OA, as ranked in the reports of WHO in 2011, is comparable with cardiac dysrhythmias, liver cirrhosis or stage IV kidney disease [7].

At present, the clinical first-line management strategies of knee OA include nonsurgical and surgical treatments [8]. Nonsurgical management methods recommended by Osteoarthritis Research Society International (OARSI) guidelines are mainly pharmacological treatments combined with core treatments such as arthritis education, exercise and weight loss [9]. Functional foods such as olive tree phenolic compounds and vitamin D, and moderate physical activity not only reduce the morbidity of knee OA by enhancing the function of the skeletal muscle system and by anti-inflammatory, antimicrobial, immunomodulatory function, but also delay the knee OA progression at early stage and speed up disease recovery [1,10,11]. Pharmacological interventions, including topical non-steroidal anti-inflammatory drugs (NSAIDs), duloxetine, tramadol, intra-articular (IA) corticosteroids and IA hyaluronic acid, can only relieve inflammation symptoms and have temporary analgesic efficacy to some extent, but cannot repair degraded cartilage or reverse disease progression [12,13]. Surgical methods include joint replacement surgery for end-stage knee OA, knee osteotomy for people with unicompartmental knee OA, and arthroscopic knee surgery [4]. However, surgical methods somewhat have a higher risk of failure and arthroscopy knee surgery increases the risk of joint replacement surgery [14,15]. And, postsurgical pain is common among the patients with total knee replacement surgery, 44% of which experience persistent pain for a long time, resulting in disability eventually [16]. Therefore, better therapeutic methods are urgently needed to be explored for cartilage restoration.

Mesenchymal stem cells (MSCs), have a potential to differentiate into osteocytes, chondrocytes and adipocytes *in vitro*, and are emerging as a perfect candidate in the field of regenerative medicine [17]. MSCs, which can be isolated from bone marrow, adipose, umbilical cord blood, umbilical cord, peripheral blood and so on, have the capacity of immune modulation, anti-inflammation, paracrine and stimulation of angiogenesis [18–21]. Moreover, MSCs from various sources present different characteristics in proliferation, multipotency, cytokine secretion and cell surface markers [22]. MSCs, especially adipose-derived mesenchymal stem cells (ADMSCs) and bone marrow-derived mesenchymal stem cells (BMSCs), have been most frequently applied in cartilage regeneration of patients with knee OA in clinical trials, although exhibiting differences in treatment effect [23,24].

Although published meta-analyses have evaluated the therapeutic effect of MSCs on knee OA, the results are inconsistent mainly because of the following possible causes [25–27]. First, poor-quality clinical trials such as single-arm trials were included in those meta-analysis. Second, MSCs from different sites were mixed for analysis. Last, treatment period, an important factor affecting the therapeutic effect, was not seriously taken into account. What is more, new randomized controlled trials (RCTs) have been published recently. It is important to update the clinical evidences of MSCs application in knee OA treatment. Therefore, the present meta-analysis, only including RCTs, is performed to assess separately and compare the therapeutic efficacy of ADMSCs and BMSCs for knee OA at the same follow-up time, so that the provided evidence can be regarded as the guidance for further investigations of MSCs in knee OA clinical application.

Materials & methods

Literature search strategy

There are the two questions to be answered by this meta-analysis. First, “*are MSCs effective in treating patients with knee OA?*” and second, “*which is better between BMSCs and ADMSCs?*” This review was prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines [28].

We searched for relevant studies or clinical trials with the following terms: (‘knee osteoarthritis’ OR ‘KOA’ OR ‘Knee OA’ OR ‘knee degenerative joint disease’) AND (‘mesenchymal stem cell’ OR ‘MSC’ OR ‘mesenchymal stromal cell’ OR ‘mesenchymal progenitor cell’) searched in [Title/Abstract], without other search restrictions. The electronic databases we searched included PubMed (2003 to September 2019), Embase (2003 to September 2019), Web of Science (2001 to September 2019), Cochrane Library (2008 to September 2019). Additionally, we looked through the references cited by other relevant review articles as a supplement to the search results and clinical trial register (clinicaltrials.gov) for unpublished completed clinical trials.

Inclusion & exclusion criteria

The literatures would be included in the meta-analysis if it met the following criteria: patients with knee OA were treated with *in vitro* cultured BMSCs or ADMSCs; RCTs, comparing stem cell transplantation therapy with traditional conservative treatment or placebo but not cartilage transplantation, were published in English language; at least one of the quantitative indicators mentioned in the result section of this meta-analysis was reported before and after treatment. These types of literatures were excluded, such as case reports/series, animal experimental studies, experiments *in vitro*, letters to the editor, review articles, conference abstracts and so on.

Data extraction

Two researchers (X Han and F Zou) reviewed the titles and abstracts of all references to identify qualified articles initially and then read the full text to further evaluate independently. Subsequently, they extracted and summarized the data from the included researches using the prepared data abstraction template. If there were any disagreements, discussions were conducted with another researcher (B Yang).

The extracted information contained in the form consisted of the following contents: the first author, year of publication, clinical trial phase, knee OA grade, cell source, age of patients, injection dose of cells, number of patients enrolled, intervention methods of experimental and control group, efficacy outcomes and follow-up time. Although efficacy outcomes varied among articles, the data of those with outcomes were extracted: Visual Analog Scale (VAS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Lysholm knee scale (Lysholm), Tegner activity scale (Tegner), in which the improvement was defined as the mean changes from baseline. In order to standardize the VAS scores from different studies, the scales were converted into a scale of 0–10.

Quality assessment

Risk of bias assessment was performed to evaluate the overall quality of literatures included in this meta-analysis using Cochrane Collaboration's risk of bias tool for RCTs [29]. Given that the total number of literatures was less than ten, it was inappropriate to use a funnel plot for publication bias. The level of evidence of RCTs was rated according to criteria provided by the Centre for Evidence-Based Medicine in Oxford, UK [30].

Statistical analysis

If more than one experimental group were reported in some clinical trials, each experimental group versus control group was selected for the analysis. The mean $\pm$ standard deviation (SD) of score differences between the follow-up time and baseline was analyzed to assess the therapeutic effects of MSCs. When the data provided in the literature were not mean or SD, but median or interquartile, an approximate estimate was made using the method described by Wan *et al.* [31]. Correlation of 0.5 was used to evaluate SD.

Statistical heterogeneity between the clinical trials was assessed via the I^2 statistics, $I^2 \leq 20\%$, low heterogeneity; $20\% < I^2 \leq 50\%$, moderate heterogeneity; $I^2 > 50\%$, substantial heterogeneity. Random- or fixed-effect models were used to estimate MSCs treatment effect based on heterogeneity. The weighted mean difference with 95% CI was utilized to reflect the continuous outcomes. $p \leq 0.05$ was regarded to be statistically significant in all the analyses. Data analyses were conducted with Review Manager 5.2.

Results

Identification of trials

The process of search, inclusion and exclusion is shown in Figure 1. A total of 1489 references were obtained in electronic database, which consisted of 266 from PubMed, 306 from Embase, 118 from Cochrane library, 794 from Web of Science and 5 from the published meta-analysis. After duplicates were removed, 1133 references remained, 894 of which consisted of 25 case studies, 210 reviews, 320 animal experiments, 325 experiments *in vitro* and 14 others. Two hundred and thirty references were further excluded because they were not knee OA, not RCTs, not BMSCs or ADMSCs therapy. Eventually, only nine RCTs published between 2012 and 2019 met the inclusion criteria [32–40].

Study characteristics

Among nine RCTs, five clinical trials focused on the treatment of knee OA with BMSCs while the remaining four studies focused on the treatment of knee OA with ADMSCs. These clinical trials involved a total of 377

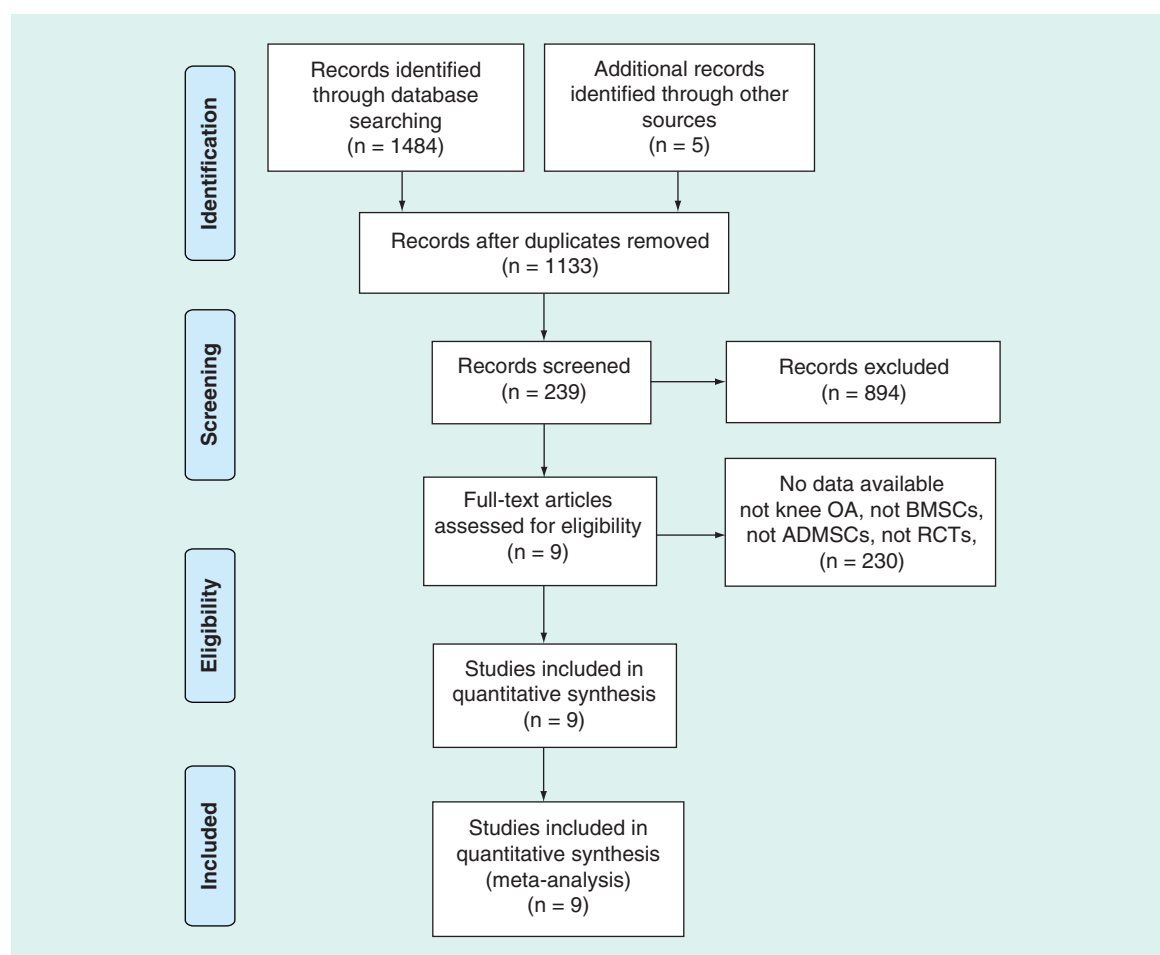


Figure 1. Flow diagram of literatures selection process.

ADMSC: Adipose derived mesenchymal stem cell; BMSC: Bone marrow derived mesenchymal stem cell; OA: Osteoarthritis; RCT: Randomized controlled trial.

patients with knee OA, 70 of which received allogeneic BMSCs injection, 48 of which received autologous BMSCs injection, and 82 of which received autologous ADMSCs injection. The dose of cells injected ranged from 1.89 to 200 million. The patients with knee OA received single intra-articular (sIA) injection in seven clinical trials, and two IA injections in two clinical trials. Nine clinical trials compared the difference in treatment effect between MSCs injection and hyaluronic acid injection, platelet-rich plasma injection, or conventional conservative management such as simple analgesia, weight management and exercise. There was one clinical trial performing arthroscopic, two clinical trials performing high tibial osteotomy and one clinical trial performing partial medial meniscectomy. The characteristics of included references are summarized in [Table 1](#).

Assessment for risk of bias

A summary for the quality assessment of included literature is shown in [Figure 2](#). The original clinical trial protocols registered on [clinicaltrials.gov](#) did not report the primary outcomes to be measured, thus there was not enough information to judge the reporting bias for the studies of [36,38–40]. Furthermore, the patients involved in these trials were not blinded to experimental intervention. For the study of [32], the outcomes reported in the literature were different from the original protocols. Therefore, the study was rated as high risk of reporting bias. Meanwhile, there was no available information about the blinding of participants and personnel in the literature. The blinding of outcome assessment was not performed in [38] and [36], which was regarded as high risk of detection bias.

Level of evidence of RCTs is summarized in [Table 1](#) according to criteria provided by the Centre for Evidence-Based Medicine in Oxford, UK. The clinical studies of [33], [37] and [34] were rated as level 1b, because the

Table 1. Summary of the eligible randomized controlled trials.

Study (year)	Clinical trial Phase	Level of evidence	K-L grade	Source (donor)	Study group	Control group	Outcome measure in meta-analysis	F-U (months)	Ref.
Lamo-Espinosa <i>et al.</i> (2016)	I/II	2b	2 to 4	BM (Auto)	N = 10, 4 males, age: median 65.9; sIA injection of 10×10^6 MSCs + 60 mg HA	N = 10, 7 males, age: median 60.3; sIA injection of 60 mg HA	VAS WOMAC	6, 12	[32]
					N = 10, 8 males, age: median 57.8; sIA injection of 100×10^6 MSCs + 60 mg HA				
Gupta <i>et al.</i> (2016)	II	1b	2 to 3	BM (Allo)	N = 10, 3 males, age: 58.1 ± 8.23 ; sIA injection of 25×10^6 MSCs + 20 mg HA	N = 10, 0 males, age: 54.90 ± 8.27 ; sIA injection of placebo + 20 mg HA	VAS WOMAC	6, 12	[33]
					N = 10, 2 males, age: 57.3 ± 9.45 ; sIA injection of 50×10^6 MSCs + 20 mg HA				
Vega <i>et al.</i> (2015)	I/II	1b	2 to 4	BM (Allo)	N = 15, 6 males, age: 56.6 ± 9.24 ; sIA injection of 40×10^6 MSCs	N = 15, 5 males, age: 57.3 ± 9.09 ; sIA injection of 60 mg HA	VAS WOMAC	12	[34]
Vangsness Jr <i>et al.</i> (2014)	I/II	1b	–	BM (Allo)	N = 18, 11 males, age: 44.6 ± 9.82 ; sIA injection of 50×10^6 MSCs + 20 mg HA	N = 19, 13 males, age: 47.8 ± 8 ; sIA injection of 20 mg HA	VAS Lysholm	6, 12, 24	[35]
					N = 18, 14 males, age: 45.6 ± 12.42 ; sIA injection of 150×10^6 MSCs + 20 mg HA				
Wong <i>et al.</i> (2013)	II	2b	–	BM (Auto)	N = 28, 15 males, age: median 53; HTO, microfracture with sIA injection of $14.6 \pm 2.9 \times 10^6$ MSCs + HA	N = 28, 14 males, age: median 49; HTO, microfracture with sIA injection of HA	Tegner Lysholm	6, 12, 24	[36]
Lu <i>et al.</i> (2019)	IIb	1b	1 to 3	AD (Auto)	N = 26, 3 males, age: 55.03 ± 9.19 ; two IA injections of 50×10^6 MSCs at 0, 3 weeks and sham injection at 1 and 2 weeks	N = 26, 3 males, age: 59.64 ± 5.97 ; four IA injections of 25 mg HA at 0, 1, 2 and 3 weeks	VAS WOMAC	6, 12	[37]
Koh <i>et al.</i> (2014)	II	2b	2 to 4	AD (Auto)	N = 21, 5 males, age: 54.2 ± 2.9 ; HTO with MSCs and PRP injection	N = 23, 6 males, age: 52.3 ± 4.9 ; HTO with PRP injection	VAS Lysholm	12, 24, 4	[38]
Koh <i>et al.</i> (2012)	II	2b	1 to 4	AD (Auto)	N = 25, 8 males, age: 54.2 ± 9.3 ; arthroscopic with 1.89×10^6 MSCs and PRP injection	N = 25, 8 males, age: 54.4 ± 11.3 ; arthroscopic with PRP injection	VAS Tegner Lysholm	16.4	[39]
Freitag <i>et al.</i> (2019)	II	2b	2 to 3	AD (Auto)	N = 10, 7 males, age: 54.6 ± 6.3 ; sIA injection of 100×10^6 MSCs	N = 10, 5 males, age: 51.5 ± 6.1 ; ongoing conventional conservative management	WOMAC	6, 12	[40]
					N = 10, 4 males, age: 54.7 ± 10.2 ; two IA injections of 100×10^6 MSCs at 0 and 6 months				

Age was showed as mean $\pm$ standard deviation or median.

AD: Adipose derived; Allo: Allogeneic; Auto: Autologous; BM: Bone marrow; F-U: Follow-up; HA: Hyaluronic acid; HTO: High tibial osteotomy; IA: Intra-articular; K-L: Kellgren and Lawrence grading scale of severity of knee OA; Lysholm: Lysholm knee scale; MSCs: Mesenchymal stem cells; N: Number of patients; PRP: Platelet-rich plasma; SD: Standard deviation; sIA: Single intra-articular; Tegner: Tegner activity scale; VAS: Visual analog scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis index.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Freitag <i>et al.</i> (2019)	+	+	-	?	+	?	+
Gupta <i>et al.</i> (2016)	+	+	+	+	+	+	+
Koh <i>et al.</i> (2012)	+	+	-	?	+	?	-
Koh <i>et al.</i> (2014)	+	+	-	-	+	?	+
Lamo-Espinosa <i>et al.</i> (2016)	+	+	?	+	+	-	+
Lu <i>et al.</i> (2019)	+	+	+	+	+	+	+
Vangsness Jr <i>et al.</i> (2014)	+	+	+	+	-	?	+
Vega <i>et al.</i> (2015)	+	+	+	+	+	+	+
Wong <i>et al.</i> (2013)	+	+	-	-	+	?	+

Figure 2. Summary of assessment for risk of bias.

methodological quality was perfect as described in Figure 2. There was performance bias or detection bias in the clinical investigations reported by [40], [38], [39] and [36], and even the reporting bias was unclear, so those RCTs were rated as level 2b. The research of [32] was rated as level 2b for unclear performance bias and existed reporting bias.

Visual analog scale

The analysis of data from 3 studies evaluating the 6-month VAS improvement, 2 of which contained a total of 84 patients (55 BMSCs and 29 controls), 1 of which contained a total of 78 patients (52 ADMSCs and 26 controls), showed a statistically significant difference between MSCs and control groups (BMSCs vs controls: MD = -1.64; 95% CI: -2.09 to -1.19; p < 0.00001; I² = 32%; ADMSCs vs controls: MD = -1.85; 95% CI: -2.83 to -0.87; p = 0.0002; I² = 0%; Figure 3A).

The analysis of data from 6 studies evaluated the 12-month VAS improvement, 4 of which contained a total of 144 patients (90 BMSCs and 54 controls) and 2 of which contained a total of 128 patients (77 ADMSCs and 51 controls). The results showed a statistically significant difference between MSCs and control groups (BMSCs vs controls: MD = -1.78; 95% CI: -2.49 to -1.07; p < 0.00001; I² = 41%; ADMSCs vs controls: MD = -1.38; 95% CI: -2.48 to -0.28; p = 0.01; I² = 62%; Figure 3B).

The analysis of data from 2 studies evaluated the 24-month VAS improvement, 1 of which contained a total of 54 patients (35 BMSCs and 19 controls) and another contained a total of 44 patients (21 ADMSCs and 23 controls). The results showed a statistically significant difference between MSCs and control groups (BMSCs vs controls: MD = -2.59; 95% CI: -3.01 to -2.18; p < 0.00001; I² = 0%; ADMSCs vs controls: MD = -0.49; 95% CI: -0.84 to -0.14; p = 0.006; Figure 3C).

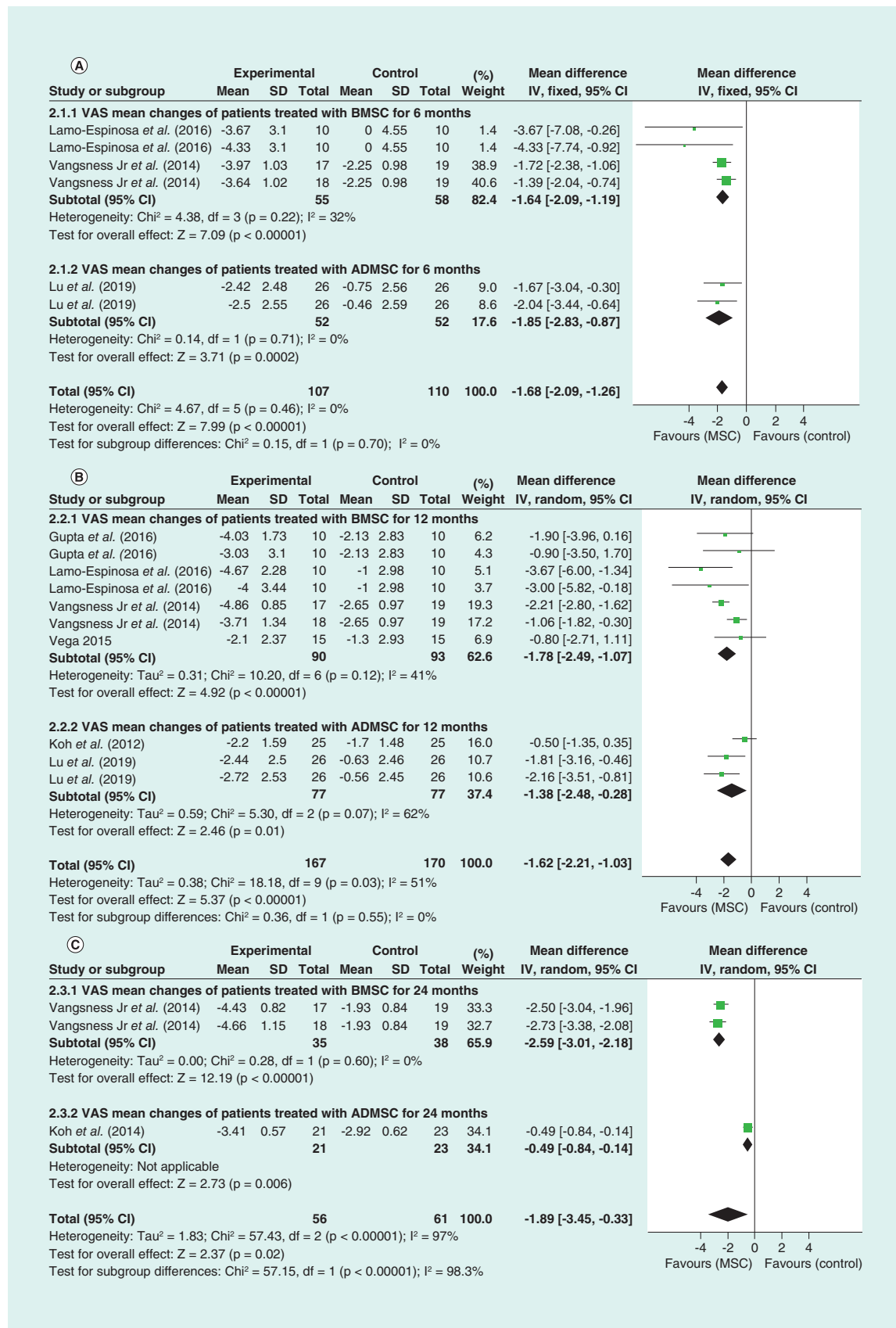


Figure 3. Forest plots of WMD for comparison of VAS scores. The forest plots of WMD with 95% CI were made for comparison of VAS scores between patients treated with bone marrow-derived mesenchymal stem cells or adipose-derived mesenchymal stem cells and controls at: **(A)** 6 months, **(B)** 12 months and **(C)** 24 months.

BMSC: Bone marrow derived mesenchymal stem cell; IV: Intravenous; MSC: Mesenchymal stem cells; SD: Standard deviation; VAS: Visual analogue scale; WMD: Weight mean difference.

Western Ontario & McMaster Universities Osteoarthritis Index

The analysis of data from 3 studies evaluated the 6-month WOMAC improvement, 1 of which contained a total of 30 patients (20 BMSCs and 10 controls) and 2 of which contained a total of 82 patients (46 ADMSCs and 36 controls). There was no significant difference between BMSCs and control groups (MD = 6.51; 95% CI: -2.38 to 15.40; $p = 0.15$; $I^2 = 0\%$; Figure 4A), but a statistically significant difference between ADMSCs and control groups (MD = -10.02; 95% CI: -19.94 to -0.10; $p = 0.05$; $I^2 = 47\%$) (Figure 4A).

The analysis of data from 5 studies evaluated the 12-month WOMAC improvement, 3 of which contained a total of 90 patients (55 BMSCs and 35 controls) and 2 of which contained a total of 82 patients (46 ADMSCs and 36 controls). There was no significant difference between BMSCs and control groups (MD = -6.81; 95% CI: -13.94 to 0.33; $p = 0.06$; $I^2 = 0\%$; Figure 4B), but a statistically significant difference between ADMSCs and control groups (MD = -19.39; 95% CI: -38.04 to -0.74; $p = 0.04$; Figure 4B).

Lysholm knee scale

The analysis of data from 3 studies evaluated the 12-month Lysholm improvement, 2 of which contained a total of 110 patients (63 BMSCs and 47 controls) and 1 of which contained a total of 50 patients (25 ADMSCs and 25 controls). It showed no significant difference between MSCs and control groups (BMSCs vs controls: MD = 1.93; 95% CI: -11.52 to 15.38; $p = 0.78$; $I^2 = 69\%$; ADMSCs vs controls: MD = 7.50; 95% CI: -1.94 to 16.94; $p = 0.12$; Figure 5A).

The analysis of data from 3 studies evaluated the 24-month Lysholm improvement, 2 of which contained a total of 110 patients (63 BMSCs and 47 controls) and 1 of which contained a total of 44 patients (21 ADMSCs and 23 controls). It showed a statistically significant difference between BMSCs and control groups (MD = 8.94; 95% CI: 1.45–16.43; $p = 0.02$; $I^2 = 36\%$; Figure 5B), but no significant difference between ADMSCs and control groups (MD = 5.10; 95% CI: -3.02 to 13.22; $p = 0.22$; Figure 5B).

Tegner activity scale

The analysis of data from 2 studies evaluated the 12-month Tegner improvement, 1 of which contained a total of 56 patients (28 BMSCs and 28 controls) and another contained a total of 50 patients (25 ADMSCs and 25 controls). It showed no significant difference between MSCs and control groups (BMSCs vs controls: MD = 0.30, 95% CI: -0.32 to 0.92; $p = 0.35$; ADMSCs vs controls: MD = 0.50, 95% CI: -0.04 to 1.04; $p = 0.07$; Figure 6).

Discussion

The therapeutic effect of MSCs on cartilage regeneration has been preliminarily confirmed through knee OA models in sheep, rabbit, rat, beagle and pig [41]. At the same time, increasing numbers of clinical trials have been performed to further investigate the MSCs-based cytotherapy for patients with knee OA, but the results are still controversial [26,42]. It has been reported in series of literatures that MSCs from different tissue or even from the same tissue are not identical in the characteristics of transcriptome patterns and immunophenotype, which is ignored by the existing meta-analysis, resulting in the unexplainable and conflicting conclusion [43,44]. BMSCs and ADMSCs are most widely used in the treatment of knee OA because of their relative accessibility, so we perform the current meta-analysis based on the published RCTs, to verify respectively and compare the effect of BMSCs and ADMSCs on knee OA.

This meta-analysis obtained the following results. First, the improvement of VAS scores was statistically significant after BMSCs treatment at 6-, 12- and 24-month follow-up compared with control groups (Figure 3). In contrast, the improvement of WOMAC scores was of no statistical significance, but there was a positive trend with the prolongation of the follow-up time (Figure 4). Lysholm scores presented a similar pattern (Figure 5). Second, VAS and WOMAC scores of patients after ADMSCs treatment were statistically significant at any follow-up time (Figures 3 & 4). The improvement of Lysholm scores was of no statistical significance compared with control groups, although treatment outcome at 12-month follow-up was better than that at 24-month follow-up, which was debatable because only data of one clinical trial were pooled in the analysis (12-month: MD = 7.50; 95% CI: -1.94 to 16.94; $p = 0.12$; 24-month: MD = 5.10; 95% CI: -3.02 to 13.22; $p = 0.22$). Finally, the results of this meta-analysis indicated that ADMSCs were more suitable for the treatment of knee OA by comparing the statistical results of VAS and WOMAC scores, although ADMSCs and BMSCs were both potential therapy methods. The statistical analysis results were summarized in Table 2.

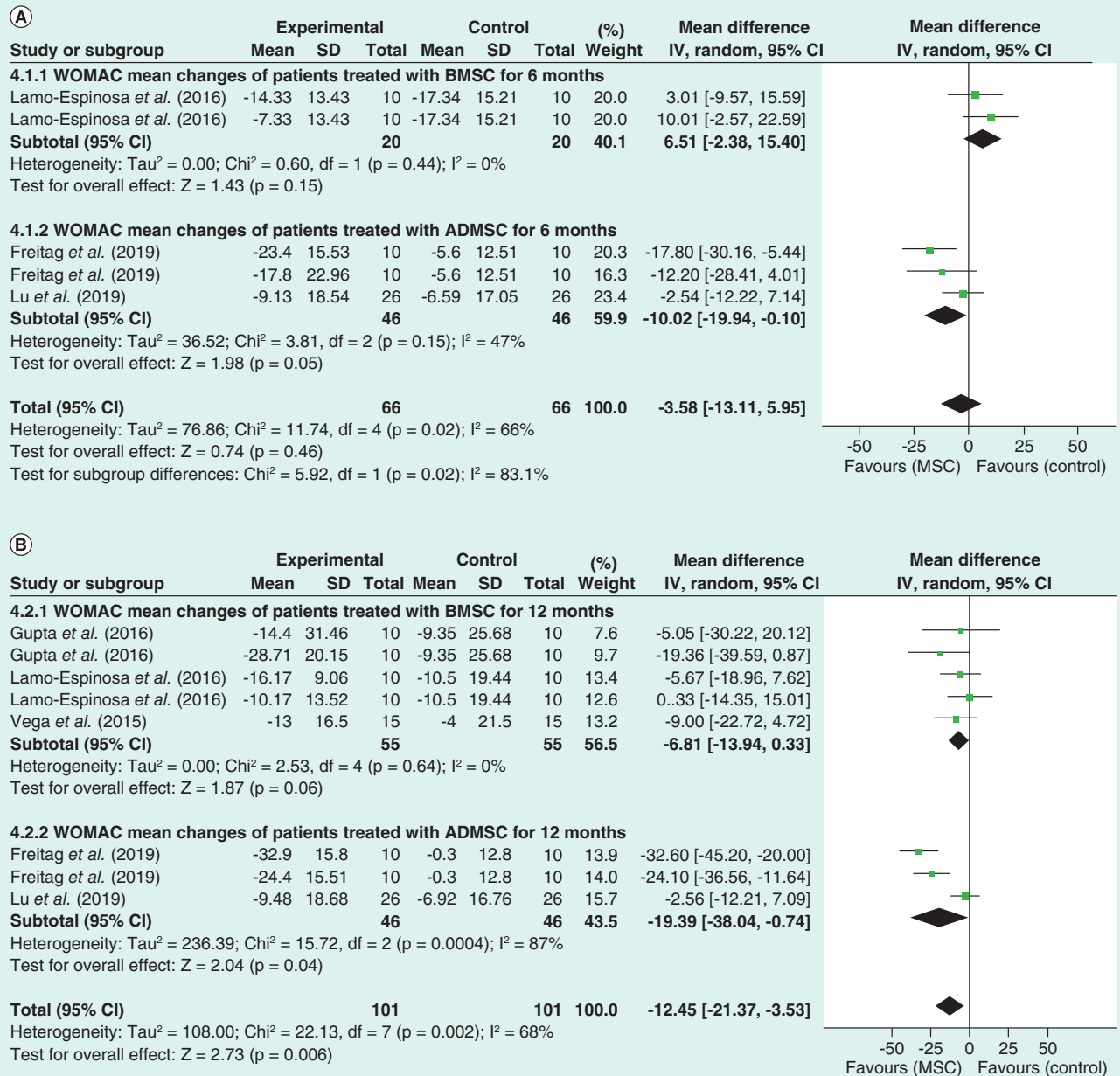


Figure 4. Forest plots of WMD for comparison of WOMAC scores. The forest plots of WMD with 95% CI were made for comparison of WOMAC scores between patients treated with bone marrow-derived mesenchymal stem cells or adipose-derived mesenchymal stem cells and controls at: **(A)** 6 months and **(B)** 12 months.

ADMSC: Adipose derived mesenchymal stem cells; BMSC: Bone marrow derived mesenchymal stem cell; IV: Intravenous; MSC: Mesenchymal stem cell; SD: Standard deviation; WMD: Weight mean difference; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

Our results of meta-analysis showed that the treatment effect of ADMSCs on patients with knee OA was better than that of BMSCs, which was consistent with what reported in [24]. The following points could explain this result. First, the immunosuppressive capacity of ADMSCs was stronger than that of BMSCs because the number of CD163⁺ macrophages (an immunoregulation phenotype) increased by co-cultured with ADMSCs but not

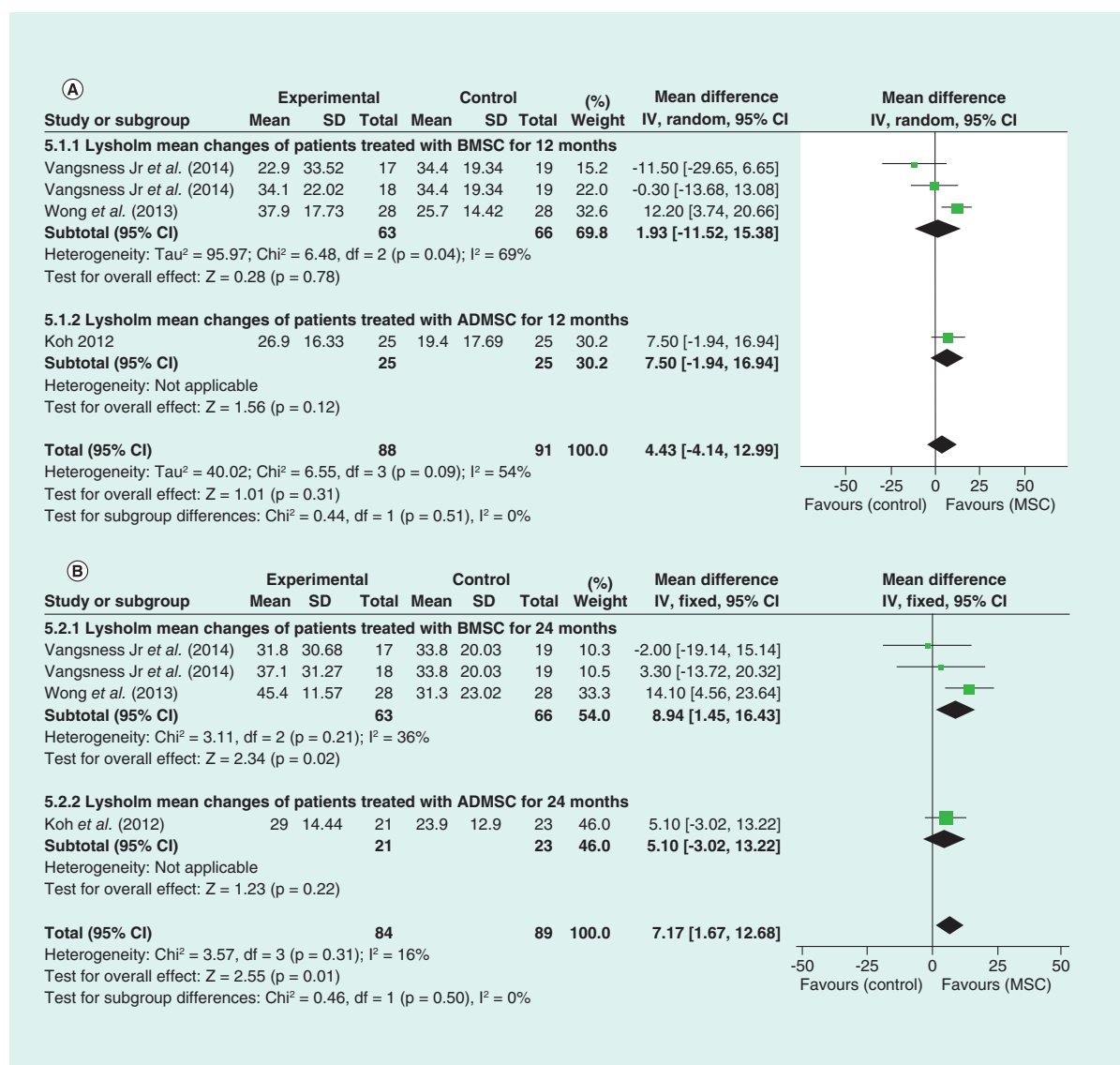


Figure 5. Forest plots of WMD for comparison of Lysholm scores. The forest plots of WMD with 95% CI were made for comparison of Lysholm scores between patients treated with bone marrow-derived mesenchymal stem cells or adipose-derived mesenchymal stem cells and controls at: **(A)** 12 months and **(B)** 24 months.

IV: Intravenous; Lysholm: Lysholm knee scale; SD: Standard deviation; WMD: Weight mean difference.

Table 2. Summary of the statistical analysis results.

MSCs	Follow-up time	VAS		WOMAC		Lysholm		Tegner	
		MD (95% CI)	p-value	MD (95% CI)	p-value	MD (95% CI)	p-value	MD (95% CI)	p-value
BMSCs	6 months	-1.64 (-2.09, -1.19)	<0.00001	6.51 (-2.38, 15.40)	0.15	—	—	—	—
	12 months	-1.78 (-2.49, -1.07)	<0.00001	-6.81 (13.94, 0.33)	0.06	1.93 (-11.52, 15.38)	0.78	0.30 (-0.32, 0.92)	0.35
	24 months	-2.59 (-3.01, -2.18)	<0.00001	—	—	8.94 (1.45, 16.43)	0.02	—	—
ADMSCs	6 months	-1.85 (-2.83, -0.87)	0.0002	-10.02 (-19.94, -0.10)	0.05	—	—	—	—
	12 months	-1.38 (-2.48, -0.28)	0.01	-19.39 (-38.04, -0.74)	0.04	7.50 (-1.94, 16.94)	0.12	0.50 (-0.04, 1.04)	0.07
	24 months	-0.49 (-0.84, -0.14)	0.006	—	—	5.10 (-3.02, 13.22)	0.22	—	—

ADMSCs: Adipose-derived mesenchymal stem cells; BMSCs: Bone marrow-derived mesenchymal stem cells; Lysholm: Lysholm knee scale; MD: Mean difference; MSC: Mesenchymal stem cell; Tegner: Tegner activity scale; VAS: Visual analog scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

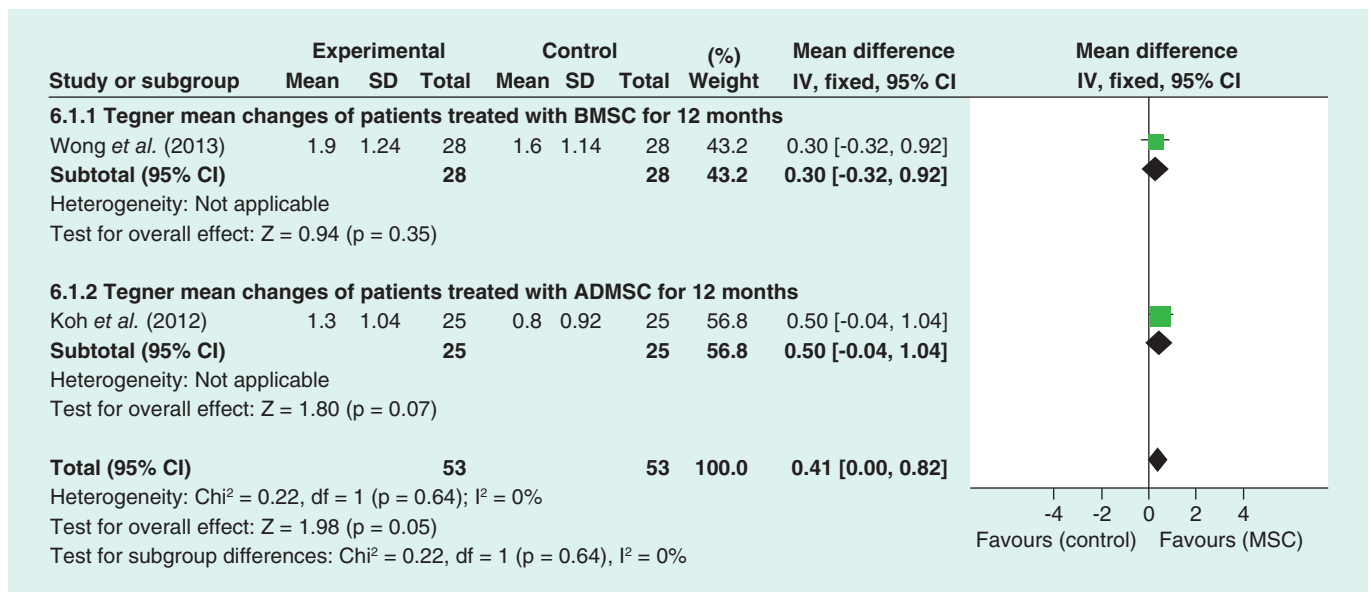


Figure 6. Forest plots of WMD for comparison of Tegner scores. The forest plots of WMD with 95% CI were made for comparison of Tegner scores between patients treated with bone marrow-derived mesenchymal stem cells or adipose-derived mesenchymal stem cells and controls at 12 months.

BMSC: Bone marrow derived mesenchymal stem cell; IV: Intravenous; MSC: Mesenchymal stem cells; SD: Standard deviation; Tegner: Tegner activity scale; WMD: Weight mean difference.

with BMSCs under low-serum conditions [45]. And, the expression of CD146, a candidate markers for MSCs stemness, decreased significantly after the proliferation of BMSCs up to passage 3–4, suggesting that BMSCs entered senescence, while major fraction of the ADMSCs did not show the signs of senescence even after passage 6–8 [43]. Finally, the results of single-cell RNA sequencing analysis indicated that the expression of genes associated with function in protein binding, growth factor, or cytokine activity in extracellular compartments was higher in ADMSCs than BMSCs, and ADMSCs had a lower expression level of human leukocyte antigen class I antigen and was less dependent on mitochondrial respiration for energy production than BMSCs [24,44]. Taken together, the evidence showed that ADMSCs were superior to BMSCs in the treatment of knee OA.

There were several limitations in our meta-analysis. First, due to only one clinical trials' data were pooled in the analysis of Lysholm and Tegner scores of patients treated with ADMSCs, it was difficult to draw solid conclusions according to the under-represented results (Figures 5 & 6). Second, differences in the dose of MSCs injected and the number of injections were not taken into account in the meta-analysis. The dose of MSCs injected varied from 1.89 to 200 million and in the two of nine selected clinical trials, two intra-articular injections were performed during the treatment procedure. Third, the scores of these indicators such as VAS, WOMAC, Lysholm and Tegner would be affected by subjective feelings, although patients were told to fill out questionnaires truthfully.

Although MSCs have shown potential therapeutic effects in the treatment of knee OA, there are still many problems to be solved such as unclear treatment mechanisms, optimal source of MSCs, recommended dose for cell injection, stem cell preparation methods and so on. This meta-analysis can provide a brighter direction for further exploration in order to advance the clinical application of stem cells.

Conclusion

There are 9 eligible RCTs involving a total of 377 patients meeting the inclusion criteria. This meta-analysis shows that regeneration with BMSCs or ADMSCs has a great application potential in the treatment of patients with knee OA. And ADMSCs tend to be superior to BMSCs according to the limited clinical evidences available, which provides references for further clinical studies in the selection of stem cell sources. Furthermore, treatment duration having a significant effect on treatment outcome, should be taken into consideration seriously by investigators in future clinical work. Nonetheless, the conclusion of this meta-analysis should be further confirmed by higher-quality, multicenter, larger sample sizes of clinical trials for the application of MSCs treatment in knee OA.

Summary point

- Knee osteoarthritis (OA), the most common chronic degenerative joint disease, accompanied by pain, stiffness, swelling and functional disability, is predicted to become the fourth leading cause of disability by 2020.
- Novel treatment methods are urgently needed to reverse the pathologic progression of knee OA, characterized by cartilage damage, synovial inflammation and osteophytes formation.
- Mesenchymal stem cells (MSCs) are widely used in the field of regenerative medicine, as they are capable of proliferation and differentiation into osteocytes, chondrocytes and adipocytes.
- Numerous preclinical and clinical trials have been conducted to explore if MSCs are effective in treating knee OA, since MSCs have the functions of anti-inflammation, immunomodulation and paracrine.
- Some meta-analyses showed that MSCs are effective in the treatment of patients with knee OA, while others suggested that the effectiveness remains to be determined.
- Our meta-analysis of randomized clinical trials shows that adipose-derived mesenchymal stem cell (ADMSC)- or bone marrow-derived mesenchymal stem cell (BMSC)-based regeneration therapy has great potential as a candidate in the treatment of patients with knee OA, and ADMSCs tend to be superior to BMSCs.
- Some researchers showed that ADMSCs are superior to BMSCs in terms of immunosuppressive capacity, MSCs stemness and the expression of genes encoding proteins, which was associated with function in protein binding, growth factor or cytokine activity in extracellular compartments.
- The conclusion of this meta-analysis should be further confirmed by higher-quality, multicenter, larger sample sizes of clinical trials for the application of MSCs treatment in knee OA.

Author contributions

X Han designed the meta-analysis protocol. X Han, F Zou and B Yang participated in the data extraction, analysis and drafted the manuscript. J Sun supervised the work and revised the manuscript.

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