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WJO mainly publishes articles reporting research results and findings obtained in the field of orthopedics and covering a wide range of topics including arthroscopy, bone trauma, bone tumors, hand and foot surgery, joint surgery, orthopedic trauma, osteoarthropathy, osteoporosis, pediatric orthopedics, spinal diseases, spine surgery, and sports medicine.

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META-ANALYSIS

Comparative effectiveness of adipose-derived mesenchymal stromal cells in the management of knee osteoarthritis: A meta-analysis

Sathish Muthu, Sandesh C Patil, Naveen Jeyaraman, Madhan Jeyaraman, Prakash Gangadaran, Ramya Lakshmi Rajendran, Eun Jung Oh, Manish Khanna, Ho Yun Chung, Byeong-Cheol Ahn

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Abstract

BACKGROUND

Osteoarthritis (OA) is the most common joint disorder, is associated with an increasing socioeconomic impact owing to the ageing population.

AIM

To analyze and compare the efficacy and safety of bone-marrow-derived mesenchymal stromal cells (BM-MSCs) and adipose tissue-derived MSCs (AD-MSCs) in knee OA management from published randomized controlled trials (RCTs).

METHODS

Independent and duplicate electronic database searches were performed, including PubMed, EMBASE, Web of Science, and Cochrane Library, until August 2021 for RCTs that analyzed the efficacy and safety of AD-MSCs and BM-MSCs in the management of knee OA. The visual analog scale (VAS) score for pain, Western Ontario McMaster Universities Osteoarthritis Index (WOMAC), Lysholm score, Tegner score, magnetic resonance observation of cartilage repair tissue score, knee osteoarthritis outcome score (KOOS), and adverse events were analyzed. Analysis was performed on the R-platform using OpenMeta (Analyst) software. Twenty-one studies, involving 936 patients, were included. Only one study compared the two MSC sources without patient randomization; hence, the results of all included studies from both sources were pooled, and a comparative critical analysis was performed.

RESULTS

At six months, both AD-MSCs and BM-MSCs showed significant VAS improvement ($P = 0.015$, $P = 0.012$); this was inconsistent at 1 year for BM-MSCs ($P < 0.001$, $P = 0.539$), and AD-MSCs outperformed BM-MSCs compared to controls in measures such as WOMAC ($P < 0.001$, $P = 0.541$), Lysholm scores ($P = 0.006$; $P = 0.933$), and KOOS ($P = 0.002$; $P = 0.012$). BM-MSC-related procedures caused significant adverse events ($P = 0.003$) compared to AD-MSCs ($P = 0.673$).

CONCLUSION

Adipose tissue is superior to bone marrow because of its safety and consistent efficacy in improving pain and functional outcomes. Future trials are urgently warranted to validate our findings and reach a consensus on the ideal source of MSCs for managing knee OA.

Key Words: Mesenchymal stromal cell; Adipose tissue-derived mesenchymal stromal cell; Bone-marrow derived mesenchymal stromal cell; Cartilage regeneration; Knee osteoarthritis; Meta-analysis; Efficacy; Safety

Core Tip: With the ongoing rise in the exploration of the clinical efficacy of mesenchymal stromal cells (MSCs) in the management of osteoarthritis (OA), there is an imminent need to identify the ideal source of MSCs to be utilized. Our meta-analysis has brought out the lacunae in the literature for studies to evaluate the impact of the source of MSCs in the management of OA. From a single-arm meta-analysis of available studies on the two commonly used sources such as bone marrow (BM) and adipose tissue, we found the adipose tissue to be superior to BM concerning the safety and consistent efficacy in improving pain and functional outcomes. However, considering the paucity of evidence, we recommend future trials to validate our findings and reach a consensus on the ideal source of MSCs for managing knee OA.

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INTRODUCTION

Osteoarthritis (OA) of the knee is the world's leading cause of degenerative joint disease leading to

articular cartilage damage resulting in pain, stiffness, and loss of joint mobility[1]. Owing to the hypovascular and aneural nature, the articular cartilage has a decreased integrity for intrinsic repair mechanisms[2]. The management of OA knee aims to provide painless functional joint with a full range of motion. To minimize the morbidity in the surgical management of OA knee, regenerative and translational medicine has paved a way to manage the articular cartilage defects with orthobiological products due to the limited potential for redifferentiation of chondrocytes[3,4].

Cell-based therapy has revolutionized its usage in the area where disease-modifying pharmacological agents or biological therapies are unavailable to treat the disorders. Mesenchymal stromal cells (MSCs) have proven the benefits in the formation of articular cartilage in the OA knee[5,6]. There are various sources of MSCs available namely bone marrow (BM), adipose tissue, synovium, peripheral blood, placenta, menstrual fluid, and amniotic fluid where the regenerative potential of all these sources of MSCs varies[7]. Out of all these sources of MSCs, the most commonly used sources are BM and adipose tissue for cartilage regeneration.

Adipose tissue possesses higher stem cell yield than BM[8]. One gram of adipose tissue yields approximately 0.35-1 million MSCs whereas one gram of BM yields 500-50000 MSCs[9]. BM-derived MSCs (BM-MSCs) show early senescence during expansion than adipose-derived MSCs (AD-MSCs)[10]. Mohamed-Ahmed *et al*[11] have demonstrated that AD-MSCs continued to proliferate up to 21 d than BM-MSCs and AD-MSCs showed considerable chondrogenic capacity, but less than BM-MSCs. Im *et al*[12] stated that osteogenic and chondrogenic potentials of BM-MSCs and AD-MSCs differ. The difference in potentiality exponentiated when an equal amount of bioactive factors are seeded and AD-MSCs demonstrated inferior regenerative potential to differentiate into bone and cartilage when compared with BM-MSCs[12]. However, Jeyaraman *et al*[13] demonstrated the efficacy, safety, and superiority of AD-MSCs transplantation when compared to BM-MSCs in OA knee management. With the conflicting evidence in literature[14-16], we aim to critically analyze the clinical efficacy and patient safety in the use of BM-MSCs and AD-MSCs in the management of OA of the knee.

MATERIALS AND METHODS

We conducted this meta-analysis in accordance with the guidelines from the Back Review Group of Cochrane Collaboration[17] and we followed the reporting guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[18].

Search strategy

We conducted an independent and duplicate electronic literature search for studies evaluating the ideal source of MSC therapy for knee OA. The literature databased searched the relevant studies include: PubMed, EMBASE, Web of Science, Reference Citation Analysis, and the Cochrane Library up to August 2021. We did not apply any language or date restrictions to the search query. We used the following keywords in the search strategy "Knee Osteoarthritis", "Knee Degeneration", "Stem Cell Therapy" and "Mesenchymal Stromal Cells", "Bone marrow", "Adipose". We have presented a sample search strategy utilized for retrieving the relevant studies from one of the included databases in Supplementary Table 1. Apart from the above databases, we also searched to identify studies not identified in the primary search from the reference list of potential articles shortlisted. Based on the criteria identified as a priori for inclusion and exclusion of studies, eligible studies were identified and included for meta-analysis. In case of discrepancy among the reviewers in study selection, discussion was made until a consensus was obtained. PRISMA flow diagram of the selection of the studies included in the analysis is given in Figure 1.

Inclusion criteria

Studies were included for quantitative review if they met the following PICOS criteria: Population: Patients with OA of knee. Intervention: AD-MSC therapy. Comparator: BM-MSC therapy. Outcomes: Visual analog score (VAS) for Pain, Western Ontario McMaster Universities Osteoarthritis Index (WOMAC), Lysholm Knee Scale (Lysholm), Magnetic resonance observation of cartilage repair tissue (MOCART) Score, knee osteoarthritis outcome score (KOOS), Tegner Activity Score (TAS) and reported adverse events. Study design: Randomized controlled trials.

Exclusion criteria

We excluded studies from analysis if they were of the following characteristics: (1) *In-vitro* studies involving stem cell therapy; (2) Studies of observational nature and interventional studies without appropriate comparison group; (3) Studies conduction animal models of knee OA investigating stem cell therapy; and (4) Review articles and *in-vitro* studies involving stem cell therapy.

Data extraction

We made an independent and duplication extraction of the following data from the included studies: (1) Study characteristics: Name of the author, publication year, country, total number of patients enrolled in

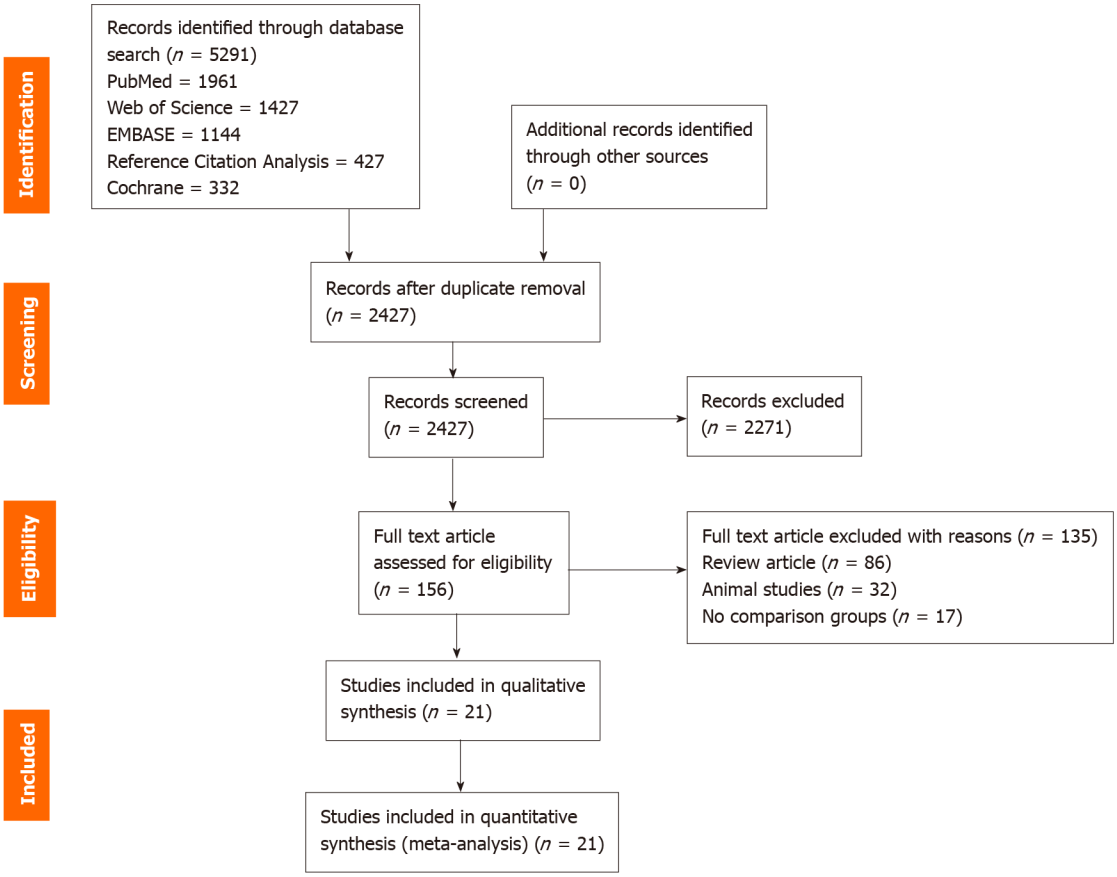

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Figure 1 PRISMA flow diagram of the included studies.

the study and level of evidence of the study; (2) Baseline characteristics: Age (mean with standard deviations), gender proportions of the individual groups, Kellgren Lawrence grades of OA, type of MSC source used in them, protocol of intervention utilised for both the groups, mean duration of follow-up of the study population and parameters used for assessment of clinical measures. We grouped studies utilizing BM based therapies involving BM concentrates and isolated expanded BM-MSCs into one group and another group involving studies using stromal vascular fraction (SVF) and isolated expanded AD-MSCs; (3) Efficacy outcomes: Pain outcomes using VAS, functional outcomes using WOMAC score, Lysholm score, KOOS, TAS, and radiological outcomes like MOCART score; (4) Safety outcomes: Reported adverse events; and (5) In case of any disagreement in data collection, discussion was made until a consensus was attained.

Risk of bias and quality assessment

We performed an independent and duplicate analysis of the methodological quality of the included studies by two reviewers based on the ROB2 tool of Cochrane Collaboration for randomized studies. The tool has five domains of bias assessment including randomization process followed in the studies, bias in application of the intended intervention, bias in the presentation of the study outcome data, bias in the measurement of measured outcome, and bias in reporting of results of the study[19].

Statistical analysis

We performed the analysis in the R platform using OpenMeta(Analyst) software[20]. We used risk ratio (RR) with 95% confidence interval (CI) for analysing dichotomous variable outcomes and weighted mean difference (WMD) with 95%CI for continuous variable outcomes. We analysed the heterogeneity observed in the results analysed using the I^2 test [21]. We used fixed-effects model to evaluate the outcomes if the value of $I^2 < 50\%$ and $P > 0.1$. We used random-effects model if the value of $I^2 > 50\%$ and $P < 0.1$. We considered a P-value < 0.05 to be significant. We performed sensitivity analyses in case of heterogeneity among the reported results from the studies included for analysis. We used Funnel plot, Egger regression test, and normal quantile plot to analyse the publication bias for the outcomes in the included studies.

RESULTS

Search results

Our initial electronic database screening yielded 4864 articles, which upon removal of the duplicate articles resulted in 2427 articles. We then performed title and abstract screening and shortlisted 156 eligible articles and excluded 2271 articles. We made a full-text review of the 156 articles qualified articles and excluded 135 of them for the reasons listed in the PRISMA flow diagram for study selection (Figure 1). Among the included studies, we found only one study by Estrada *et al*[22] to make a direct comparison of the adipose tissue and BM as a source of MSC and found no significant difference among the groups compared despite observing a significant improvement from the baseline. The study had a selective allocation of the subjects based on the stage of the disease and utilized adipose tissue-based cellular therapy for high-grade disease and BM-based therapy for intermediate grade disease and platelet-based therapy for early disease. To objectively evaluate the results of the study across all the grades of disease, we pooled the results of all the included studies of both sources and made a combined comparative quantitative analysis of all 21 included studies[22-42] with 936 patients. 9/21 studies[22,26,27,29,31,36-40] utilized MSC of adipogenic origin, of which 1 study utilized AD-MSC of allogenic source while rest 8 studies utilized AD-MSCs of autogenous source. 12/21 studies[22-25,28,30,32-35,41,42] utilized MSC of BM origin, of which 2 studies utilized BM-MSCs of allogenic sources, and the rest 10 studies utilized autogenous sources of BM-MSC. We did not note a standardised utilization of the dose of the MSCs transplanted in the included studies. We did not note uniformity among the included studies for the measures of outcomes assessment employed. We presented the general characteristics of the included studies in Table 1. The protocol of intervention used in the case and control groups along with the measures of outcome assessment were given in Table 2.

Quality assessment

We utilised RoB2 tool for the evaluation of the methodological quality of the included studies and presented in Figure 2. We did not note the included studies to have high risk of bias to warrant exclusion from the analysis.

Efficacy outcomes

Visual analog scale for pain: We analysed 7 studies[16,17,21,26-28,30], 5 studies[26,27,31,36,40], and 1 study[39] reporting the VAS outcome at 6, 12, and 24 mo respectively using adipose tissue as the source of MSCs. There was a significant heterogeneity observed between the included studies. (I^2 > 80%, P < 0.001). Hence, the random-effects model was used for analysis across all time points. On analysis, significant reduction in VAS score was noted compared to their controls at 6 mo [WMD = -13.414, 95%CI: (-24.175)-(-2.653), P < 0.015; Figure 3A], 12 mo [WMD = -21.498, 95%CI: (-33.819)-(-9.177), P < 0.001; Figure 3B), and 24 mo [WMD = -6.000, 95%CI: (-9.079)-(-2.921), P < 0.05; Figure 3C] compared to their controls as shown in Figure 3. Similarly, we analysed 5 studies[24,25,28,32,33], 4 studies[23,24,28,33], and 1 study[24] reporting the VAS outcome at 6, 12, and 24 mo respectively using BM as the source of MSCs. There was a significant heterogeneity observed between the included studies. (I^2 > 80%, P < 0.001). Hence, the random-effects model was used for analysis across all time points. On analysis, significant reduction in VAS score was noted compared to their controls at 6 mo [WMD = -11.028, 95%CI: (-19.605)-(-2.450), P < 0.012; Figure 3A), and 24 mo [WMD = -17.589, 95%CI: (-22.486)-(-12.692), P < 0.001; Figure 3C), with a drop in the pain control at 12 mo [WMD = -2.366, 95%CI: (-9.912)-5.180, P = 0.539; Figure 3B], period compared to their controls.

On critical analysis of the pain reduction potential of both the sources, it is noted as shown in Figure 4 that despite the inconsistency in the pain reduction at 12 mo with BM, we noted a rising trend curve in pain reduction which favors the therapy. Although both the sources were capable of significant pain reduction compared to their controls, adipose tissue demonstrated consistent results across all the time points. However, the inconsistencies in the results of BM could also be accounted to the heterogeneity in the studies included for analysis.

WOMAC score: We analyzed 6 studies[27,31,36,37,39,40], and 6 studies[27,31,36-39] reporting the WOMAC scores at 6, and 12 mo respectively using adipose tissue as the source of MSCs. There was a significant heterogeneity observed between the included studies. (I^2 > 80%, P < 0.001). Hence, the random-effects model was used for analysis across all time points. On analysis, significant reduction in WOMAC scores were noted compared to their controls at 6 mo [WMD = -21.317, 95%CI: (-27.146)-(-15.488), P < 0.001; Figure 3D], and 12 mo [WMD = -19.341, 95%CI: (-30.544)-(-8.138), P < 0.001; Figure 3E] compared to their controls as shown in Figure 3. Similarly, we analyzed 7 studies[24,25,28,32-35], and 6 studies[24,25,28,33-35] reporting the WOMAC outcome at 6, and 12 mo respectively using BM as the source of MSCs. There was a significant heterogeneity observed between the included studies (I^2 > 80%, P < 0.001). Hence, the random-effects model was used for analysis across all time points. On analysis, we did not note any significant reduction in WOMAC scores compared to their controls at 6 mo [WMD = -1.958, 95%CI: (-10.273)- 6.357, P = 0.644; Figure 3D], and 12 mo [WMD = -1.944, 95%CI: (-8.183)-4.294, P = 0.541; Figure 3E] compared to their controls.

Table 1 Characteristics of included studies

Sl. No	Ref.	Country	Nature of study	Kellgren Lawrence Grade	Sample size	Treatment/ control	Mean age (SD)		Male/female		MSC type	MSC source	Follow-up (mo)
							Treatment group	Control group	Treatment group	Control group			
1	Vega *et al*[23], 2015	Spain	RCT	II, III, IV	30	15/15	56.6 ± 9.24	57.3 ± 9.09	06/09	05/10	BM	Allo	12
2	Vangsness *et al*[24], 2014	United States	RCT	NR	55	36/19	44.6 ± 9.82	47.8 ± 8	25/11	13/06	BM	Allo	24
3	Garay-Mendoza *et al*[25], 2018	Mexico	RCT	NR	61	30/31	55.57 ± 12.02	59.32 ± 10.85	07/23	09/22	BM	Auto	6
4	Kuah *et al*[26], 2018	Australia	RCT	I, II, III	20	16/4	50.8 ± 7.29	55.0 ± 10.42	11/05	01/03	AD	Allo	12
5	Estrada *et al*[22], 2020	Argentina	RCT	I, II, III	89	60/29	61 ± 12	61 ± 12	NR	NR	BM / AD	Auto	12
6	Freitag *et al*[27], 2019	Australia	RCT	II, III	30	20/10	54.6 ± 6.3	51.5 ± 6.1	11/09	01/09	AD	Auto	12
7	Ruane *et al*[41], 2021	United States	RCT	I, II, III	32	17/15	58.06 ± 9.14	58.6 ± 8.05	09/08	10/05	BM	Auto	12
8	Lamo-Espinosa *et al*[28], 2016	Spain	RCT	II, III, IV	30	20/10	65.9	60.3	12/08	07/03	BM	Auto	12
9	Garza *et al*[29], 2020	United States	RCT	II, III	39	26/13	60.5 ± 7.9	57.1 ± 9.1	15/11	7/6	AD	Auto	12
10	Wong *et al*[30], 2013	Singapore	RCT	NR	56	28/28	53	49	15/13	14/14	BM	Auto	24
11	Lu *et al*[31], 2019	China	RCT	I, II, III	53	27/26	55.03 ± 9.19	59.64 ± 5.97	03/24	03/23	AD	Auto	12
12	Lv *et al*[42], 2015	Huang	RCT	I, II	80	40/40	55.9 ± 8.1	55.1 ± 6.8	14/26	13/27	BM	Auto	12
13	Emadedin *et al*[32], 2018	Iran	RCT	II, III, IV	43	19/24	51.7 ± 9.2	54.7 ± 5.3	12/07	15/09	BM	Auto	6
14	Gupta *et al*[33], 2016	India	RCT	II, III	60	40/20	58.10 ± 8.23	54.90 ± 8.27	12/28	4/16	BM	Allo	12
15	Bastos *et al*[34], 2020	Brazil	RCT	I, II, III, IV	47	30/17	55.7 ± 7.8	55.9 ± 13.4	15/15	09/08	BM	Auto	12
16	Wakitani *et al*[35], 2002	Japan		I, II	24	12/12	NR	NR	NR	NR	BM	Auto	16
17	Tran *et al*[36], 2019	Taiwan	RCT	II, III	33	15/18	58.2 ± 5.70	59.0 ± 6.04	03/12	05/13	AD	Auto	24
18	Lee *et al*[37], 2019	South Korea	RCT	II, III, IV	24	12/12	62.2 ± 6.5	63.2 ± 4.2	03/09	03/09	AD	Auto	6
19	Koh *et al*[38], 2012	South Korea	RCT	IV	50	25/25	54.2 ± 9.3	54.4 ± 11.3	08/17	08/17	AD	Auto	16
20	Koh *et al*[39], 2014	South Korea	RCT	I, II, III	44	23/21	52.3 ± 4.9	54.2 ± 2.9	06/17	05/16	AD	Auto	24
21	Hong *et al*[40], 2019	China	RCT	II, III	32	16/16	51 ± 5.95	53 ± 10.97	03/13	03/13	AD	Auto	12

AD: Adipose derived; Allo: Allogenic; Auto: Autologous; BM: Bone marrow; MSC: Mesenchymal stem cell; NR: Not reported; RCT: Randomized controlled trial; SD: Standard deviation.

On critical analysis of the WOMAC score reduction potential of both the sources, it is noted as shown in Figure 3 that most of the studies that utilized BM did not report any significant improvement compared to their controls, despite their heterogeneity in results at both 6 mo and 12 mo. Since the WOMAC score concentrates more on the functional efficiency of the intervention apart from pain reduction, adipose tissue stands superior to BM as a dependable source of MSC to give better functional results consistently across both time points.

Lysholm knee score: We analyzed 3 studies[36,36,38], and one study[39] reporting the lysholm score at 12, and 24 mo respectively using adipose tissue as the source of MSCs. There was a significant heterogeneity observed between the included studies. (I^2 > 80%, P < 0.001). Hence, the random-effects model was used for analysis across all time points. On analysis, significant improvement in scores was noted compared to their controls at 12 mo (WMD = 6.494, 95%CI: 1.889-11.100, P = 0.006; Figure 3F). However, at 24 mo, the improvement in scores was not sustained [WMD = 4.100, 95%CI: (-4.757)-12.9557, P = 0.757; Figure 3G] compared to their controls as shown in Figure 3. Similarly, we analyzed 3 studies[22, 24,30], and 2 studies[24,30] reporting Lysholm scores outcome at 12 and 24 mo respectively using BM as the source of MSCs. There was a significant heterogeneity observed between the included studies. (I^2 > 80%, P < 0.001). Hence, the random-effects model was used for analysis across all time points. On analysis, we did not note any significant improvement in Lysholm score compared to their controls at both 12 mo [WMD = 0.232, 95%CI: (-5.133)-5.597, P = 0.933; Figure 3F], and 24 mo [WMD = 4.412, 95%CI: (-0.801)-9.626, P = 0.097; Figure 3G] respectively. On critical analysis of the improvement of the Lysholm score of both the sources, it is noted only in studies utilizing adipose tissue as the source of MSC significant improvement in the functional outcomes is noted which is in corroboration with the WOMAC score results.

KOOS & MOCART Score

We analyzed the quality of life outcomes such as KOOS reported in 3 studies[22,27,39] using adipose tissue and 3 studies[22,34,41] utilizing BM as the source of MSCs. There was a significant heterogeneity observed between the included studies (I^2 > 80%, P < 0.001). Hence, the random-effects model was used for analysis across all time points. On analysis, significant improvement in scores was noted in both adipose tissue (WMD = 13.124, 95%CI: 4.745-21.502, P = 0.002; Figure 3H) and BM (WMD = 2.642, 95%CI: 0.587-4.698, P = 0.012; Figure 3H) as the sources compared to their controls, despite the inconsistencies noted earlier in the functional outcomes such as WOMAC or Lysholm scores.

Similarly, we analyzed 2 studies that objectively analyzed the regenerate cartilage tissue using magnetic resonance imaging with MOCART score between the two sources[30,40]. There was a significant heterogeneity observed between the included studies (I^2 > 80%, P < 0.001). Hence, the random-effects model was used for analysis. We noted significant improvement in the MOCART scores at 12 mo in both the sources (WMD = 31.625, 95%CI: 7.481-55.769, P = 0.010; Figure 3I) compared to their controls. As shown in Figure 3, although both the sources had significantly improved KOOS and MOCART scores at 12 mo, the improvement noted with adipose tissues stands relatively high compared to the BM.

Table 2 Stem cell transplantation protocol of the included studies

Ref.	MSC type	MSC source	MSC preparation	MSC count (10^7 cells)	Treatment group intervention	Control group intervention	Outcome measures
Vega *et al*[23], 2015	BM	Allo	CE-BMMSC	4	sIA injection of MSC	sIA Injection of 60 mg HA	VAS, WOMAC
Vangsness *et al* [24], 2014	BM	Allo	CE-BMMSC	5/15	sIA injection of MSC + 20 mg HA	sIA Injection of 20 mg HA	VAS, Lysholm Score
Garay-Mendoza *et al*[25], 2018	BM	Auto	BMC	NA	600 μg/d G-CSF for 3 consecutive days before the procedure + sIA injection of MSC	Oral acetaminophen, 500 mg every 8 h for 6 mo	VAS, WOMAC
Kuah *et al*[26], 2018	AD	Allo	CE-ADMSC	0.39-0.67	sIA injection of MSC	Placebo sIA injection of cell culture media and cryopreservative	VAS, WOMAC, MRI assessment
Estrada *et al*[22], 2020	AD	Auto	BMC	NA	sIA injection of BM concentrate	sIA injection of PRP	IKDC, Lysholm Score, KOOS
Estrada *et al*[22], 2020	BM	Auto	SVF	NA	sIA injection of lipoaspirate	sIA injection of PRP	
Freitag *et al*[27], 2019	AD	Auto	CE-ADMSC	10	sIA injection of MSC ± 2 nd injection at 6 mo	Conservative management	VAS, WOMAC, KOOS, MRI assessment
Ruane *et al*[41], 2021	BM	Auto	BMC	NA	sIA injection of BM concentrate + PRP	Gel-One® Cross-Linked hyaluronate injection	VAS, KOOS
Lamo-Espinosa *et al*[28], 2016	BM	Auto	CE-BMMSC	1	sIA injection of MSC + 60 mg HA	sIA injection of 60 mg HA	VAS, WOMAC, MRI assessment
Garza *et al*[29], 2020	AD	Auto	SVF	NA	sIA injection of MSC	Placebo injection without cells	WOMAC, MRI assessment
Wong *et al*[30], 2013	BM	Auto	CE-BMMSC	1.46	HTO + microfracture + sIA injection of MSC + 20 mg HA	HTO + microfracture + sIA injection of 20 mg HA	Tegner Score, Lysholm Score
Lu *et al*[31], 2019	AD	Auto	CE-ADMSC	5	2 IA injection of MSC at 0, 3 wk and sham injection at 1, 2 wk	4 IA injection of 25 mg HA at 0, 1, 2, 3 wk	VAS, WOMAC
Lv *et al*[42], 2015	BM	Auto	CE-BMMSC	3.82	3 × monthly IA injection of MSC + 20 mg HA	sIA injection of 20 mg HA	Tegner Score, Lysholm Score
Emadedin *et al* [32], 2018	BM	Auto	CE-BMMSC	4	sIA injection of MSC	Placebo sIA injection of normal saline	VAS, WOMAC
Gupta *et al*[33], 2016	BM	Allo	CE-BMMSC	2.5-15	sIA injection of MSC + 20 mg HA	Placebo sIA injection of 20 mg HA	VAS, WOMAC, MRI assessment
Bastos *et al*[34], 2020	BM	Auto	CE-BMMSC	4	sIA injection of MSC in 10 mL of PRP	sIA injection of 4 mg dexamethasone	KOOS, MRI assessment
Wakitani *et al* [35], 2002	BM	Auto	CE-BMMSC	1	HTO + microfracture + sIA injection of MSC	HTO + microfracture + placebo injection	MRI assessment, HSS knee rating scale
Tran *et al*[36], 2019	AD	Auto	SVF	NA	Arthroscopic micro fracture + sIA injection of MSC	Arthroscopic micro fracture	WOMAC, MRI assessment
Lee *et al*[37], 2019	AD	Auto	CE-ADMSC	10	sIA injection of MSC	Placebo injection with normal saline	WOMAC, MRI assessment
Koh *et al*[38], 2012	AD	Auto	SVF	0.189	Arthroscopic debridement + sIA injection of MSC + PRP	Arthroscopic debridement + PRP	VAS, Tegner Score, Lysholm Score
Koh *et al*[39], 2014	AD	Auto	CE-ADMSC	0.411	HTO + sIA injection of MSC + PRP	HTO + PRP	VAS, Lysholm Score
Hong *et al*[40], 2019	AD	Auto	SVF	0.745	sIA injection of MSC	sIA injection of 40 mg HA	VAS, WOMAC, MRI assessment

AD: Adipose derived; Allo: Allogenic; Auto: Autologous; BM: Bone marrow; BMC: Bone marrow concentrate; CE-ADMSC: Culture expanded adipose

derived mesenchymal stem cell; CE-BMMSC: Culture expanded bone marrow mesenchymal stem cell; HA: Hyaluronic acid; HSS: Hospital for special surgeries; HTO: High tibial osteotomy; IA: Intra-articular; IKDC: International Knee Documentation Committee; KOOS: Knee Osteoarthritis Outcome Score; PRP: Platelet rich plasma; MRI: Magnetic resonance imaging; MSC: Mesenchymal stem cell; sIA: Single intra-articular; SVF: Stromal vascular fraction; VAS: Visual analog score; WOMAC: Western Ontario Mc-Master Universities Osteoarthritis index.

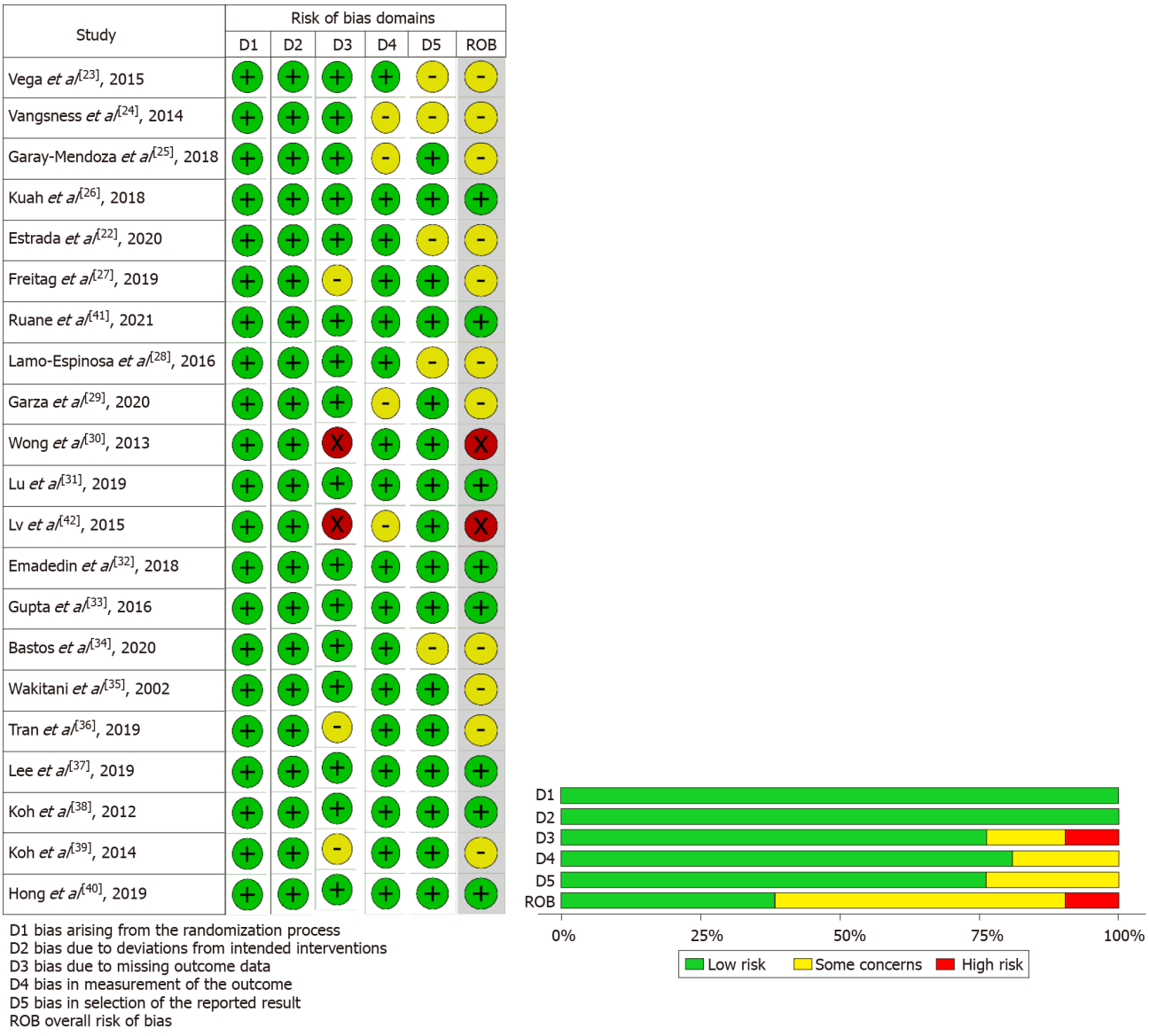

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Figure 2 Methodological quality and risk of bias assessment of all the included studies.

Safety

Seven studies involving 141 patients reported adverse effects with low heterogeneity among the included studies using adipose tissue as the source of MSC for knee OA. (I^2 = 0.0%, P = 0.968). Hence, a fixed-effects model was used for analysis. There was no significant increase in the adverse events compared to the controls (RR = 1.081, 95%CI: 0.754-1.549, P = 0.673; Figure 5).

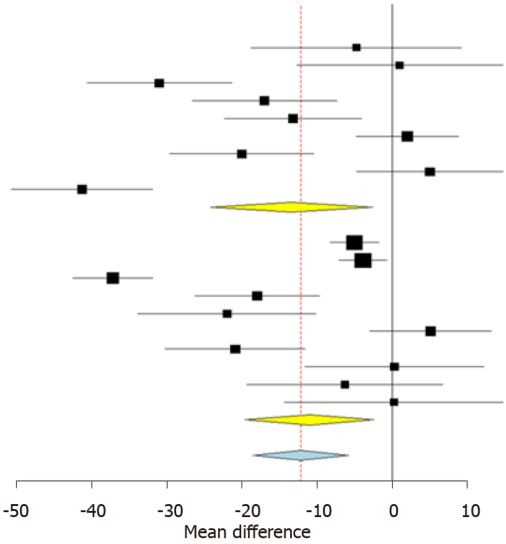
Seven studies involving 180 patients reported adverse effects with low heterogeneity among the included studies with AD-MSC (I^2 = 0.0%, P = 0.996). Hence, a fixed-effects model was used for analysis. There was no significant increase in the adverse events compared to the controls (RR = 1.072, 95%CI: 0.440-2.612, P = 0.876; Figure 5). No major serious adverse events with permanent effects such as death, tumor, or immune reaction to the intervention were noted during follow-up in either of the sources of MSCs.

Sensitivity analysis

We conducted sensitivity analysis whenever heterogeneity was noted in the outcomes analysed. The

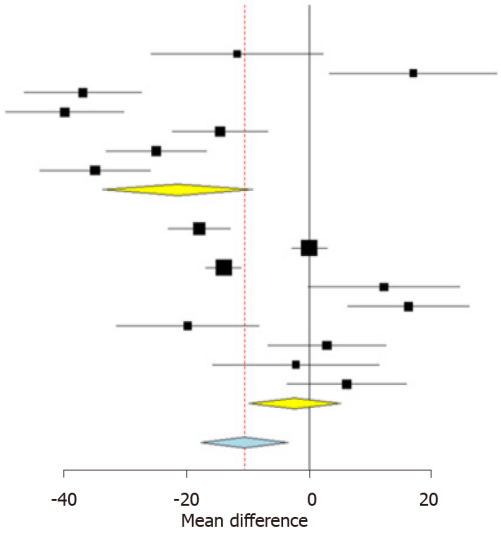
A

Study	Estimate (95%CI)
Kuah *et al*[26], 2018	-4.800 (-18.822, 9.222)
Kuah *et al*[26], 2018	1.000 (-12.696, 14.696)
Freitag *et al*[27], 2019	-31.000 (-40.642, -21.358)
Freitag *et al*[27], 2019	-17.000 (-40.642, -21.358)
Lu *et al*[31], 2019	-13.200 (-22.361, -4.039)
Tran *et al*[36], 2019	2.000 (-4.852, 8.852)
Lee *et al*[37], 2019	-20.000 (-29.602, -10.398)
Koh *et al*[38], 2012	5.000 (-4.705, 14.705)
Hong *et al*[40], 2019	-41.300 (-50.712, -31.888)
Subgroup adipose (I^2 = 90.89 %, P = 0.000)	-13.414 (-24.175, -2.653)
Vangsness *et al*[24], 2014	-5.000 (-8.223, -1.777)
Vangsness *et al*[24], 2014	-3.900 (-7.123, -0.677)
Garay-Mendoza *et al*[25], 2018	-37.200 (-42.518, -31.882)
Lamo-Espinosa *et al*[28], 2016	-18.000 (-26.269, -9.731)
Lamo-Espinosa *et al*[28], 2016	-22.000 (-33.841, -10.159)
Emadedin *et al*[32], 2018	5.100 (-2.996, 13.196)
Gupta *et al*[33], 2016	-20.900 (-30.218, -11.582)
Gupta *et al*[33], 2016	0.300 (-11.606, 12.206)
Gupta *et al*[33], 2016	-6.300 (-19.316, 6.716)
Gupta *et al*[33], 2016	0.200 (-14.309, 14. 709)
Subgroup bone marrow (I^2 = 94.17%, P = 0.000)	-11.028 (-19.605, -2.450)
Overall (I^2 = 92.68%, P = 0.000)	-12.160 (-18.539, -5.780)



B

Study	Estimate (95%CI)
Kuah *et al*[26], 2018	-11.800 (-25.822, 2.222)
Kuah *et al*[26], 2018	17.000 (3.304, 30.696)
Freitag *et al*[27], 2019	-37.000 (-46.642, -27.358)
Freitag *et al*[27], 2019	-40.000 (-49.642, -30.358)
Lu *et al*[31], 2019	-14.600 (-22.419, -6.781)
Tran *et al*[36], 2019	-25.000 (-33.223, -16.777)
Hong *et al*[40], 2019	-35.300 (-44.035, -25.965)
Subgroup adipose (I^2 = 90.93 %, P = 0.000)	-21.498 (-33.819, -9.177)
Vega *et al*[23], 2015	-18.000 (-23.061, -12.939)
Vangsness *et al*[24], 2014	-0.000 (-2.910, 2.910)
Vangsness *et al*[24], 2014	-14.000 (-16.910, -11.090)
Lamo-Espinosa *et al*[28], 2016	-12.200 (-0.218, -24.618)
Lamo-Espinosa *et al*[28], 2016	16.200 (6.255, 26.145)
Gupta *et al*[33], 2016	-19.900 (-31.528, -8.272)
Gupta *et al*[33], 2016	2.900 (-6.762, 12.562)
Gupta *et al*[33], 2016	-2.200 (-15.807, 11.407)
Gupta *et al*[33], 2016	6.100 (-3.680, 15.880)
Subgroup bone marrow (I^2 = 92.64%, P = 0.000)	-2.366 (-9.912, 5.180)
Overall (I^2 = 93.96%, P = 0.000)	-10.556 (-17.690, -3.422)



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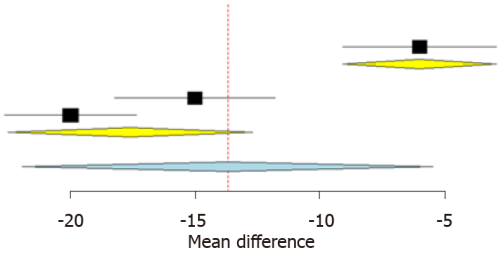
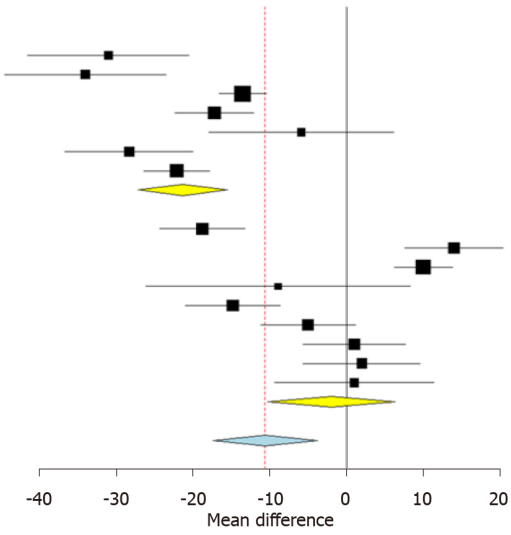
Study	Estimate (95%CI)
Koh *et al*[39], 2014	-6.000 (-9.079, -2.921)
Subgroup adipose (I^2 = NA, P = NA)	-6.000 (-9.079, -2.921)
Vangsness *et al*[24], 2014	-15.000 (-18.223, -11.777)
Vangsness *et al*[24], 2014	-20.000 (-22.641, 17.359)
Subgroup bone marrow (I^2 = 81.92%, P = 0.019)	-17.589 (-22.486, -12.692)
Overall (I^2 = 95.65%, P = 0.000)	-13.691 (-21.921, -5.461)



D

Study	Estimate (95%CI)
Freitag *et al*[27], 2019	-31.000 (-41.518, -20.482)
Freitag *et al*[27], 2019	-34.000 (-44.518, -23.482)
Lu *et al*[31], 2019	-13.500 (-16.555, -10.445)
Tran *et al*[36], 2019	-17.200 (-22.319, -12.081)
Lee *et al*[37], 2019	-5.880 (-17.909, 6.149)
Koh *et al*[38], 2012	-28.300 (-36.615, -19.985)
Hong *et al*[40], 2019	-22.100 (-26.356, -17.844)
Subgroup adipose (I^2 = 83.57 %, P = 0.000)	-21.317 (-27.146, -15.488)
Lv *et al*[42], 2015	-18.770 (-24.275, -13.265)
Vangsness *et al*[24], 2014	14.000 (7.625, 20.375)
Garay-Mendoza *et al*[25], 2018	10.000 (6.223, 13.777)
Lamo-Espinosa *et al*[28], 2016	-8.900 (-26.155, 8.355)
Emadedin *et al*[32], 2018	-14.800 (-20.974, -8.626)
Bastos *et al*[34], 2020	-5.000 (-11.161, 1.161)
Bastos *et al*[34], 2020	1.000 (-5.695, 7.695)
Wakitani *et al*[35], 2002	2.000 (-5.612, 9.612)
Gupta *et al*[33], 2016	1.000 (-9.390, 11.390)
Subgroup bone marrow (I^2 = 93.11%, P = 0.019)	-1.958 (-10.273, 6.357)
Overall (I^2 = 94.97%, P = 0.000)	-10.577 (-17.392, -3.763)



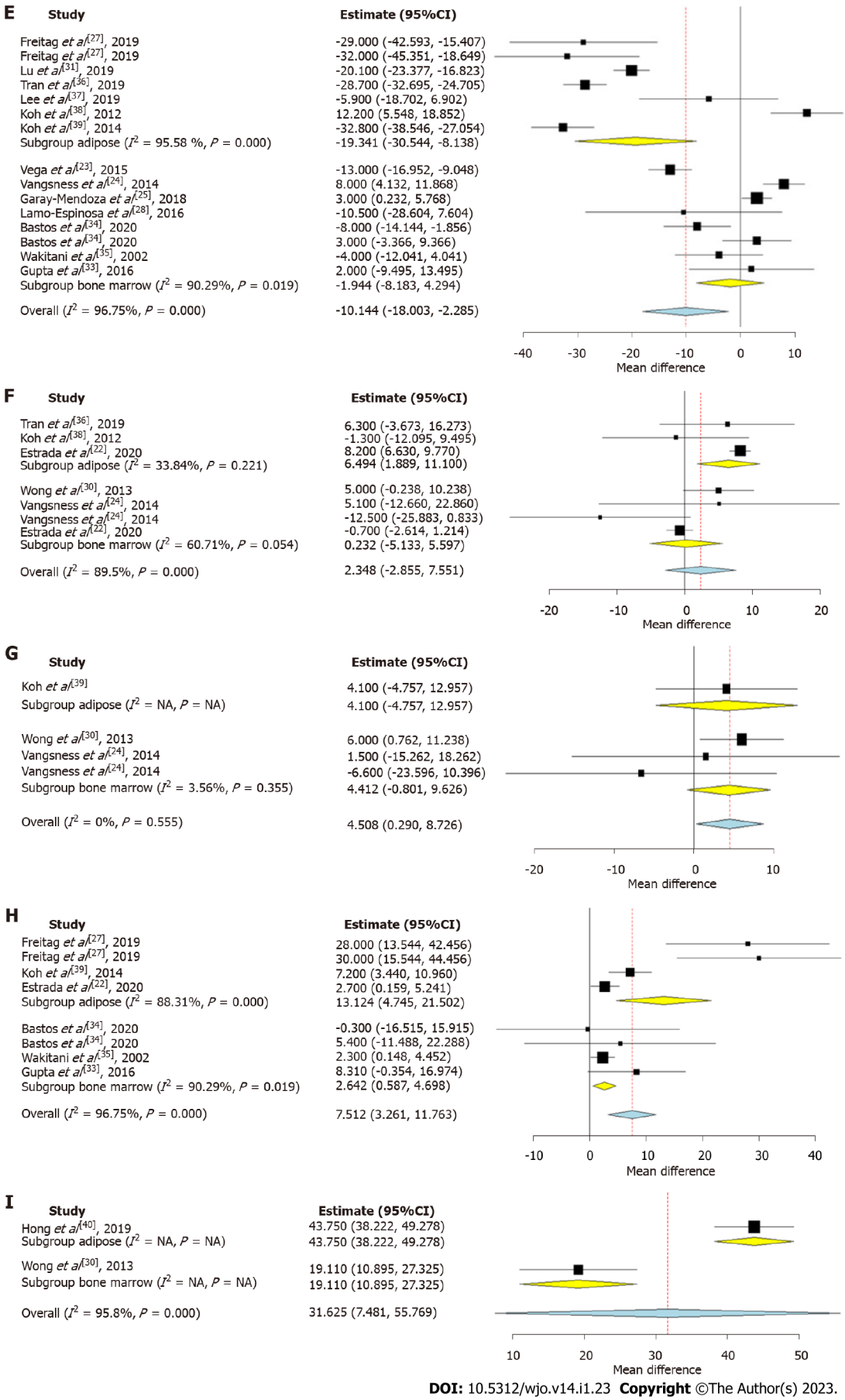


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Figure 3 Forest plot of the included studies comparing adipose tissue and bone marrow as a source of mesenchymal stromal cell therapy compared to their controls. A: Visual analog scale (VAS) at 6 mo; B: VAS at 12 mo; C: VAS at 24 mo; D: Western Ontario McMaster Universities

Osteoarthritis Index (WOMAC) at 6 mo; E: WOMAC at 12 mo; F: Lysholm at 12 mo; G: Lysholm at 24 mo; H: Knee osteoarthritis outcome score at 12 mo; I: Magnetic resonance observation of cartilage repair tissue score at 12 mo. CI: Confidence interval; NA: Not available.

results of the outcomes analysed such as VAS for pain, WOMAC, Lysholm, KOOS, MOCART, and adverse events were not significantly altered by sequentially omitting each study in the meta-analysis. We also did not note a change in the consistency of the results for the outcomes analysed upon changing the analysis to the random-effects model.

Publications bias

Publication bias was analyzed utilizing the funnel plot, normal quantile plot, and Egger's regression test for the meta-analysis performed. There was no evidence of publication bias by funnel plot and normal quantile plot as shown in Figure 6 or by Egger's regression test (P = 0.519). We noted symmetrical distribution of studies in the funnel plot and studies were found to lie close to the 95%CI and no significant heterogeneity was noted in the distribution of the studies about the axes, suggestive of minimal publication bias.

DISCUSSION

In the era of regenerative medicine, MSCs serve the ideal cell-based resort for treating cartilage disorders and provide a platform for regeneration. Various animal models have demonstrated the safety and efficacy of MSCs in cartilage regeneration. MSCs bridge a gap between pharmacological and surgical management of OA of the knee. MSCs offer a balanced equilibrium between pro-and anti-apoptotic, pro-and anti-inflammatory cytokines, and pro-and anti-angiogenic factors to maintain joint homeostasis which is required for cartilage regeneration. Though the reliability of cellular therapy for OA knee has been tested in various preclinical and clinical trials, they provide the readers with conflicting results in the source of MSCs to be used for cartilage regeneration. In literature, the ideal source of MSCs for cartilage regeneration is still under debate. The chondrogenesis among the available sources of MSCs is demonstrated in all the sources of MSCs. The most ideal chondrogenic MSC is still under question.

The efficacy of MSC in cartilage regeneration should withstand the biomechanical stress which has to be evaluated according to regulatory guidelines to demonstrate the role of cellular therapy for adoption across an expanding patient population. The reasons behind the less exploration of other sources of MSCs for chondrogenesis are inadequate standardization of isolation protocols to retrieve MSC from that particular source and the strict regulatory guidelines laid by the governing bodies. In this analysis, we tried to analyze whether BM-MSCs or AD-MSCs are the ideal sources for chondrogenesis. Among all the available sources of MSCs, extraction of MSCs from BM and adipose tissue pose minimal morbidity to the donor site while compared with other sources of MSCs. BM-MSC is the most popular source and widely used MSC for osseous and cartilage regeneration. The MSC count in BM appears to be less when compared with the MSC count in adipose tissue. Hence the source of MSC from where it is retrieved plays a major role in cartilage regeneration.

Although Estrada *et al*[22] in their study compared the two sources, they did not randomize the study participants to the interventions analyzed. Instead, they categorized the patients with severe disease to be allotted to adipose-based therapy while mild and moderate diseases to platelet- and BM-based therapy respectively. Hence one cannot objectively compare the efficacy of the two different sources, which necessitated us to undergo a pooled analysis of the studies using adipose tissue and BM as the source of MSCs in the management of knee OA and compared their results using minimum clinical importance difference (MCID) for the parameter concerned.

Main finding

We comprehensively and critically reviewed all available literature to identify the ideal source of MSCs for knee OA and found that: AD-MSCs showed a statistically significant and consistent improvement in all functional outcome measures, such as the VAS score for pain, WOMAC, Lysholm, KOOS, and radiological outcome parameters such as MOCART at varied time intervals compared to their corresponding controls. In contrast, despite better improvement in the VAS score for pain in the long term (24 mo), BM, as a source of MSCs, did not show functional benefits when evaluated using the WOMAC and Lysholm. However, objective measures of quality of life using KOOS and radiological outcome parameters, such as MOCART, showed significant benefits compared to their corresponding controls.

On comparing the relative improvement in various analyzed parameters, such as the VAS score, WOMAC, Lysholm, KOOS, and MOCART, between the two sources adipose tissue outperformed BM, with the difference in their outcome parameters more than the MCID for the concerned parameter. The MCID used were 15 for VAS score, 10 for WOMAC, 25 for Lysholm, 15 for KOOS[43,44]. There were no significant adverse events with either MSC compared to their controls.

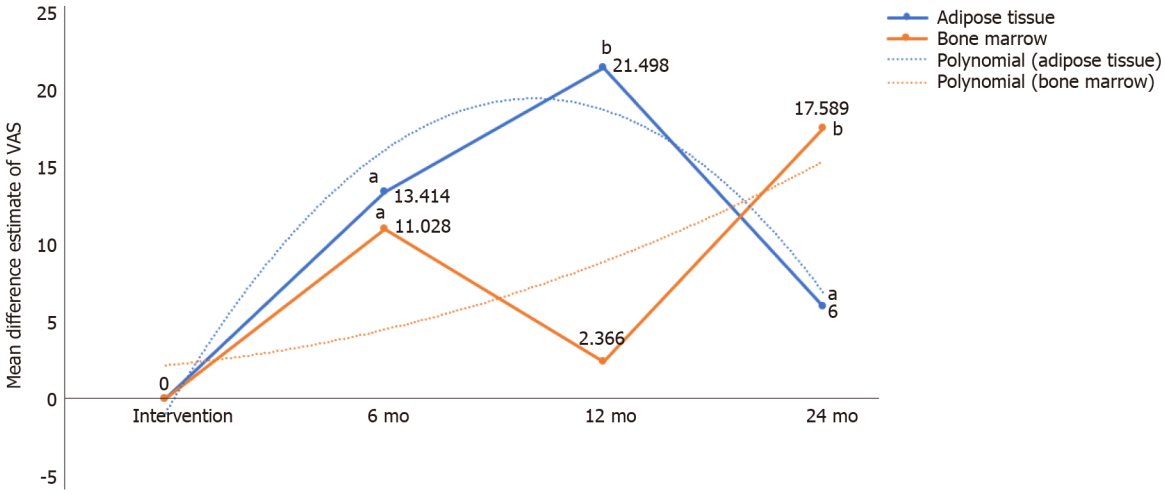

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Figure 4 Pain reduction potential of adipose tissue and bone marrow at various timepoints based on visual analog scale score. [a]*P* < 0.05; [b]*P* < 0.001. VAS: Visual analog scale.

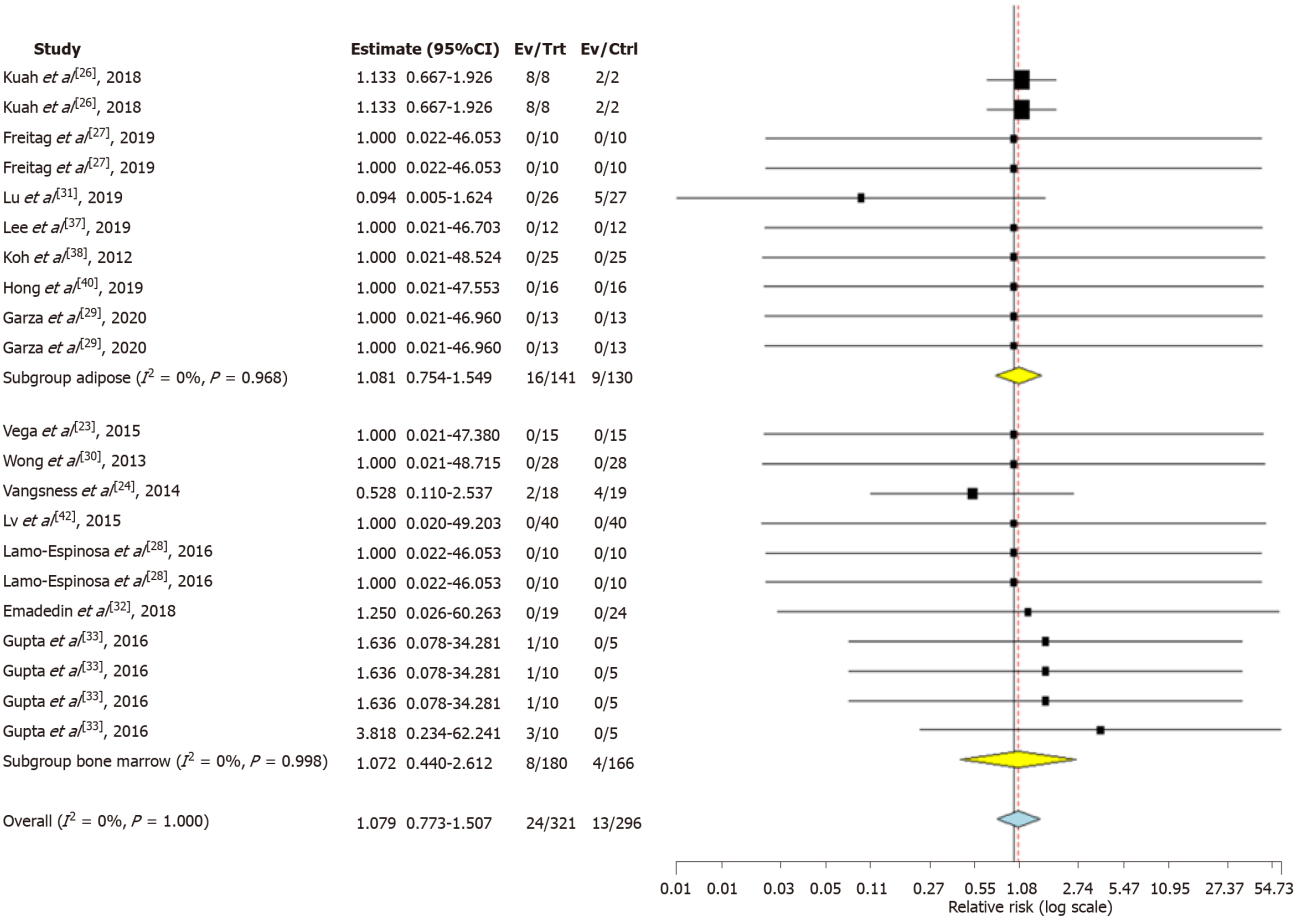

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Figure 5 Forest plot of the included studies comparing adverse events upon using adipose tissue and bone marrow as a source of mesenchymal stromal cell therapy compared to their controls. CI: Confidence interval.

MSC harvest

The source of MSC harvesting is an important factor in stem cell research. Although the BM-MSC harvesting method has been the most commonly used method of MSC harvesting, recent studies have pointed towards AD-MSC owing to their ease of extraction and lack of procedure-related morbidity [45]. Isolation of AD-MSCs from adipose tissue blocks is superior to liposuction[11]. There is a well-

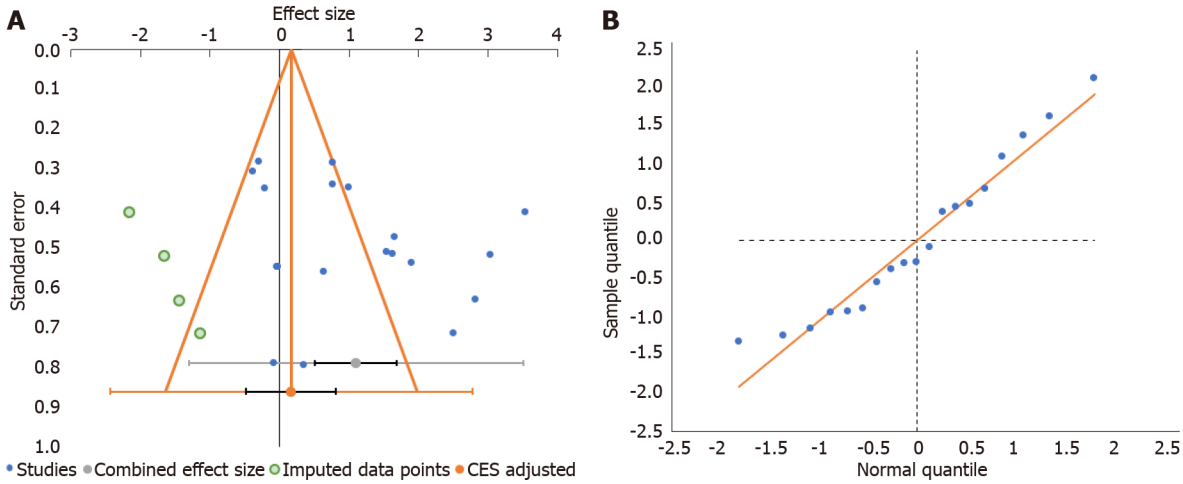

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Figure 6 Publication bias assessment. A: Funnel plot; B: Quantile plot for the visual analog score outcome at 6 mo in the included studies. CES: Combined effect size.

documented procedure for harvesting a larger number of AD-MSCs under local anesthesia with minimal procedure-related patient morbidity[46]. Although there have been reports of fat embolism during AD-MSC harvesting, its incidence is very low. With appropriate techniques and skill, the incidence can be further reduced. The ease of access to fat sources and its minimally invasive approach, unlike access to BM, is sufficient to compel researchers to further explore AD-MSC harvesting techniques.

MSC yield

Pendleton *et al*[46] reported that AD-MSCs had a higher yield than BM-MSCs. Furthermore, a higher seeding density is necessary for the successful growth and expansion of BM-MSCs. Luna *et al*[47] recovered 1×10^6 adipocytes, 1×10^6 ASCs, 1×10^6 vascular endothelial cells, and 1×10^6 other cells from 1 g of adipose tissue. Adipose tissue contains up to 3% stem and progenitor cells in the uncultured SVF, containing 2500 times more stem cells than the BM source[48,49]. SVF mixture, a derivative of adipose tissue, contains 30% MSCs, 3% endothelial cells, and 14% endothelial precursor cells[50], whereas BM-MSCs contain 0.001% MSCs, 0.1% endothelial cells, and 2% endothelial precursor cells[51].

AD-MSCs demonstrate a consistently faster proliferation rate across multiple passages[46]. While the proliferation rate of MSCs from both sources was comparable on days 3 and 7, AD-MSCs continued to proliferate significantly up to day 21, and BM-MSCs attained a plateau from day 14. Similarly, significantly higher cellular metabolic activity was noted in AD-MSCs than in BM-MSCs on days 14 and 21, indicating a higher cellular yield of MSCs[46].

MSC differentiation potential

Although AD-MSCs are harvested with minimal morbidity and provide a better yield than BM-MSCs, the ultimate target of these MSCs in orthopedic research is their differentiation potential in chondrogenic and osteogenic lineages. Chondrogenic differentiation at the gene level, determined by real-time quantitative polymerase chain reaction, showed that the expression of the chondrogenic gene aggrecan varied in AD-MSCs and BM-MSCs from different donors. However, overall, the expression was significantly higher in BM-MSCs than in AD-MSCs. There was no remarkable difference in cartilaginous proteoglycan matrix formation between AD-MSCs and BM-MSCs[11]. The expression of Runx2, collagen type I, and alkaline phosphatase increases from day 7 to day 14 in both AD-MSCs and BM-MSCs, with significantly higher expression in BM-MSCs than in AD-MSCs[11].

Despite easier harvest and superior yield from adipose tissue, AD-MSCs fall short in terms of differentiation potential in chondrogenesis or osteogenesis compared to BM-MSCs. Therefore, research to enhance the necessary lineage differentiation characteristics of AD-MSCs is ongoing to reap the full benefits of its abundant availability and ease of harvesting because AD-MSCs have a more grounded immunomodulatory impact than BM-MSCs in altering the pathological milieu of the target site[52-54].

MSC storage

Short- and long-term storage of AD-MSCs was investigated. The storage of AD-MSCs decreases their cellular proliferative capacity over time[55]. Hence, it must be supplemented with 10% human serum or PRP in 0.9% saline solution at 4 °C for the first 2 h and not more than 4 h[56,57]. For long-term storage, AD-MSCs can be stored at -80 °C in liquid nitrogen for up to 6 mo[58,59]. In contrast, BM-MSCs have been stored for more than 10 years without losing their multipotency[60].

Future directives

With the evolution in the understanding of the biology of MSCs, there is a corresponding expanding horizon of their therapeutic possibilities with their properties towards induction of angiogenesis; regulation of immune response and inflammation; modulation of cell differentiation and proliferation; extracellular matrix formation; neuroprotective and neurotrophic effects; and anti-apoptotic, anti-tumor, and anti-microbial activities[61]. Apart from identifying the ideal source of MSCs for a particular scenario, the development of methods to identify their potency is needed for objective assessment of the individual MSCs concerned to account for individual variability, which might affect the therapeutic response[62]. The future of MSC-based therapies is driving towards a cell-free secretome-based therapy using MSC-derived exosomal vesicles that exert the necessary functional activities of MSCs, where the ideal required cellular characteristics of MSCs from multiple sources could be combined to obtain the maximum benefits of the individual MSC source[63].

Limitations

Our study had certain limitations. First, we could not find data on the blinding of the intervention to the participants in most of the included studies, which could invite room for bias on the part of patients or observers. Second, we noted heterogeneity among the majority of the analyzed outcomes, which could be due to the variability in the protocols followed for intervention in the included studies, as shown in Table 2. The heterogeneity could also be attributed to the inclusion of patients with a different spectrum of disease processes or difference in the control interventions utilized across the included studies. Therefore, we recommend a large multicenter trial with a standardized dosage and intervention protocol, evaluated using established outcome measures both in the short and long term, without any adjuvant procedures to further confirm our analysis results.

CONCLUSION

Our critical analysis of the literature showed that adipose tissue is superior to BM as a source of MSC because of its safety and consistent efficacy concerning improvement in pain and functional outcomes in managing knee OA. However, future trials of sufficient quality are warranted to validate our findings to arrive at a consensus on the ideal source of MSC for use in cellular therapy for knee OA.

ARTICLE HIGHLIGHTS

Research background

Mesenchymal stromal cell (MSC)-based therapies are being commonly utilized in the context of knee osteoarthritis (OA) with promising results. The commonly used sources of the MSC remain in the bone marrow (BM) and the adipose derived (AD).

Research motivation

Despite the prevalence of the use of MSCs of varying origins in the management of knee OA, the literature is not clear on the ideal source to focus on for future research.

Research objectives

In this study, we aim to compare the efficacy and safety of the two commonly used sources of MSCs namely BM and adipose tissue in the management of knee OA.

Research methods

We conducted a systematic review and meta-analysis of the randomized controlled trials (RCTs) in the literature identified from databases such as PubMed, EMBASE, Web of Science, and Cochrane Library until August 2021 that analyzed the efficacy and safety of AD and BM-MSCs in the management of knee OA. we used outcome parameters such as the visual analog scale (VAS) score for pain, Western Ontario McMaster Universities Osteoarthritis Index (WOMAC), Lysholm score, Tegner score, magnetic resonance observation of cartilage repair tissue (MOCART) score, knee osteoarthritis outcome score (KOOS), and adverse events.

Research results

We identified twenty-one studies including 936 patients. Of all the studies included, only one study compared the two MSC sources without patient randomization; hence, the results of all included studies from both sources were pooled, and a comparative critical analysis was performed. At six months, both AD-MSCs and BM-MSCs showed significant VAS improvement (P = 0.015, P = 0.012); this was inconsistent at 1 year for BM-MSCs (P < 0.001, P = 0.539), and AD-MSCs outperformed BM-MSCs

compared to controls in measures such as WOMAC ($P < 0.001$, $P = 0.541$), Lysholm scores ($P = 0.006$; $P = 0.933$), and KOOS ($P = 0.002$; $P = 0.012$). BM-MSC-related procedures caused significant adverse events ($P = 0.003$) compared to AD-MSCs ($P = 0.673$).

Research conclusions

Our study identified adipose tissue to be superior to BM in terms of its safety and consistent efficacy in improving the pain and functional outcome parameters analyzed.

Research perspectives

We suggest for future RCTs be conducted to make a direct comparison of the two sources considering the paucity of the literature identified in this study and also to validate the findings arrived in the study.

FOOTNOTES

Author contributions: Muthu S, Patil SC, Jeyaraman N, and Jeyaraman M involved in the conception and design of the manuscript; Gangadaran P, Rajendran RL, Oh EJ, Khanna M, Chung HY, and Ahn BC contributed to the administrative support; Muthu S, Patil SC, Jeyaraman N, Jeyaraman M, and Khanna M participated in the provision of study materials or patients; Muthu S, Patil SC and Jeyaraman N involved in the collection and assembly of data; Muthu S, Patil SC, Jeyaraman N, Jeyaraman M, Gangadaran P, Chung HY, and Ahn BC analysied and interpreted data; Muthu S, Patil SC, Jeyaraman N, Jeyaraman M, Gangadaran P, Rajendran RL, Oh EJ, Khanna M, Chung HY, and Ahn BC wrote the manuscript writing; Muthu S, Chung HY and Ahn BC are co-corresponding authors of this manuscript; Gangadaran P, Rajendran RL and Chung HY contributed to the funding acquisition; and all authors have read and agreed to the published version of the manuscript.

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