First author	year	n	Mean age	% women	Last follow-up	Stem cell type	Culturing	Surgical procedure	Number of intra-articular injections	Timing of injection	Control intervention
Wong[30]	2013	int. 28, control 28	int. median 53 (range 36 to 54), control median 49 (range 24 to 54)	int. 53, control 50	int. mean 24.8 mo (range 24 to 36 mo), control mean 24.5 mo (range 24 to 35 mo)	autologous bone marrow-derived mesenchymal stem cells	yes	arthroscopic microfracture and medial opening high tibial osteotomy	1	median 22 days postoperatively	HA
Koh[31]	2014	int. 26, control 26	int. 54.2 ± 2.9, control 52.3 ± 4.9	int. 76, control 74	mean 24.4 mo (range 24 to 25 mo)	autologous adipose-derived mesenchymal stem cells	yes	arthroscopy and open-wedge high tibial osteotomy	1	peroperatively	PRP
Lamo-Espinosa[22,44]	2016	int. low-dose 10, int. high-dose 10, control 12 (2 withdrew consent)	int. low-dose median 65.9 (IQR 59.5 to 70.6), int. high-dose median 57.8 (IQR 55.0 to 60.8), control median 60.3 (IQR 55.1 to 66.1)	int. low-dose 60, int. high-dose 20, control 30	48 mo	autologous bone marrow-derived mesenchymal stem cells	yes	none	1 MSC, directly followed by 1 injection hyaluronic acid	3-4 weeks after harvesting from iliac crest	HA

Goncars[32]	2017	int. 28, control 28	int. 53.4 ± 15, control 58.6 ± 13	int. 46, control 64	12 mo	autologous bone marrow-derived mononuclear cells	no	none	int. 1, control 3 (with an interval of one week)	directly after harvesting	sodium hyaluronate
Turajane[33]	2017	int. (with GFA) 20, int. (without GFA) 20, control 20	int. (with GFA) 54.9 ± 6.1, int. (without GFA) 55.4 ± 2.3, control 54.7 ± 3.5	int. (with GFA) 50, int. (without GFA) 85, control 70	12 mo	autologous activated peripheral blood stem cells with GFA (group 1) or without (group 2) GFA, and hyaluronic acid	no	arthroscopic microdrilling mesenchymal cell stimulation procedure	3 (with an interval of one week)	Peroperatively	HA
Emadedin[34]	2018	int. 22, control 25	int. 51.7 ± 9.2, control 54.7 ± 5.3	int. 36.8, control 37.5	6 mo	autologous bone marrow-derived mesenchymal stromal cells	yes	none	1	after culturing (timing unknown)	saline
Centeno[35]	2018	int. 26 , control 22	int. 54, control 57	not reported	3 mo*	autologous bone marrow concentrate	no	none	3 (pre-treatment, intervention , post-treatment)	time between BMC procedure and injection not reported	exercise
Lee[36]	2018	int. 12, control 12	int. 62.2 ± 6.5, control 63.2 ± 4.2	int. 75, control 75	6 mo	autologous adipose tissue-derived mesenchymal stem cells	yes	none	1	Not reported	saline
Bastos[25]	2020	int. MSC 16, int. MSC+PRP 14,	int. MSC 55.7 ± 7.8, int. MSC+PRP	int. MSC 37.5, int MSC+PRP	12 mo	autologous bone marrow stromal	yes	none	1	2 to 3 weeks after bone	corticosteroid

		control 17	60.8 ± 9.9, control 55.9 ± 13.4	64.3, control 47.1		mesenchymal stem cells				marrow aspiration	
Freitag[37]	2019	int. 1 injection 10, int. 2 injections 10, control 10	int. 1 injection 54.6 (SD 6.3), int. 2 injections 54.7 (SD 10.2), control 51.5 (SD 6.1)	int. 1 injection 30, int. 2 injections 60, control 50	12 mo	autologous adipose derived mesenchymal stem cells	yes	none	1 or 2 (baseline and at 6 months)	time between harvesting and injection not reported	saline
Lu[26]	2019	int. 26, control 26	int. 55.0 (SD 9.2), control 59.6 (SD 6.0)	int. 88.5, control 88.5	12 mo	autologous mesenchymal progenitor cells derived from adipose tissue	yes	none	int. 2 with mesenchymal progenitor cells and 2 sham, control 4	1 week between injections	HA
Lamo-Espinosa[38]	2020	int. 24, control 26	int. 56 (range 40-62), control 54.6 (range 33-70)	int. 83, control 84	12 mo	autologous bone marrow-derived mesenchymal stem cells	yes	none	int. 3 (1 MSC+PRP and 2 single PRP), control 3 (all PRP)	1 week between injections	PRP
Kim[39]	2020	int. MSC 36, int. MSC+allogenic cartilage 34	int. MSC 55.6 (SD 2.9), int. MSC+allogenic cartilage 56.1 (SD 3.6)	int. MSC 58, int. MSC+allogenic cartilage 59	Mean int. MSC 27.3 mo (SD 3.3), int. MSC+allogenic cartilage 27.8 (SD 3.9)	autologous adipose derived mesenchymal stem cells	yes	open-wedge high tibial osteotomy	1	peroperatively	Allogenic cartilage

Anz[40]	2020	int. 45, control 39	int. 55.8 (SD 11.3), control 52.2 (SD 12.4)	Int. 40, control 44	12 mo	Autologous bone marrow aspirate concentrate	no	none	1	directly after harvesting	PRP

Table 1: study characteristics. Int = intervention group, mo = months, SD = standard deviation, MSC = mesenchymal stem cells, HA = hyaluronic acid, PRP = platelet-rich plasma, TKA = total knee arthroplasty, GFA = growth factor addition, BMC = bone marrow concentrate.

* after 3 months all patients crossed over to intervention group and had a follow-up of 2 years. We included results after 3 months only.

comparison	Outcome measures	No. of studies	Number of participants	Quality of evidence	Downgrading due to
	functional outcomes				
BM- MSC vs. HA	Beneficial effect of MSC therapy on functional outcome scores (e.g. KOOS, WOMAC, Tegner, Lysholm) after 1, 2 and 4 years of follow-up and results were superior compared to HA therapy.	3	142	low	study limitations (1 level), imprecision (1 level)
BM-MSC vs. saline	Improvement of WOMAC (25 points (95% CI: 16-35)) 6 months after MSC therapy and no change in the saline group. Greater improvement in walking distance 6 months after MSC therapy compared to the saline group (mean 1151 vs. 127 m).	1	43	very low	study limitations (2 levels), imprecision (1 level)
BM-MSC vs. exercise	Change score after 3 months of follow-up (MSC vs. exercise): LEAS (+0.8 vs. -1.1 points (p=0.002)), KSS knee score (12.0 vs. 0.6 points (p<0.001)) and SF-12 (4.9 vs. 2.4 points (p=0.27)).	1	48	very low	study limitations (2 levels), imprecision (1 level)
BM-MSC vs. PRP	Improvement of WOMAC total after 1 year: mean 10.4-15.9 points after MSC therapy and mean 9.6-15.3 points after PRP.	2	134	low to very low	study limitations (1 or 2 levels), imprecision (1 level)
BM-MSC+PRP vs. BM-MSC	Improvement of 24.0 points (BM-MSC) and 22.7 points (BM-MSC+PRP) on KOOS after 12 months (ns).	1	47	low	imprecision (2 levels)
BM-MSC ± PRP vs. corticosteroid	Significant improvement in the BM-MSC ± PRP group (22.6 points) on KOOS after 12 months and a non-significant change after corticosteroid injection.	1	47	low	imprecision (2 levels)

BM-MSC vs. BMC-MSC + allogenic cartilage	Lysholm score after 1 year: mean 27.6 points improvement in MSC group and mean 30.7 points in MSC + allogenic cartilage group. KOOS symptom improved with mean 24.8 and 31.9 points, respectively.	1	70	very low	study limitations (1 level), imprecision (2 levels)
AD-MSC vs. PRP	Significant greater improvement of KOOS subscales pain and function after AD-MSC therapy compared to PRP (81 vs. 74 points (pain) and 82 vs. 75 points (function)) and non-significant change and difference on other KOOS subscales.	1	44	very low	study limitations (1 level), imprecision (2 levels)
AD-MSC vs. saline	Mean reduction of WOMAC by 55% 6 months after MSC therapy. Significant improvement of KOOS on all subscales 6 months after MSC therapy (effect sizes not reported). No significant change in the saline group on WOMAC and all KOOS subscales.	1	24	low	imprecision (2 levels)
AD-MSC vs. exercise	Improvement of global WOMAC by 24.4-32.9 points 12 months after MSC therapy and significant improvement of KOOS (effect sizes not reported). No changes in the exercise group.	1	30	very low	study limitations (1 level), inconsistency (1 level), imprecision (2 levels)
AD-MSC v. HA	Both groups improved after 6 and 12 months on WOMAC and differences were not statistical significant different between groups.	1	53	low	imprecision (2 levels)
PB-MSC vs. HA	Improvement of 137.2-166.5 points on WOMAC total 12 months after MSC therapy and 88.5 points in the HA group ($p<0.001$).	1	60	very low	study limitations (2 levels), imprecision (2 levels)
	<u>pain (VAS)</u>				
BM- MSC vs. HA	Median reduction of 4-5 points on VAS (0-10) after 1 year in the MSC group and median reduction of 1 point in the HA group. After 4 years of follow-up	3	142	low	study limitations (1

	median reduction of 3-5 points in MSC group and increase of 2 points in HA group.				level), imprecision (1 level)
BM-MSC vs. saline	No difference on VAS (0-100) after 6 months between both groups (mean change -20 points (MSC) vs. -15 points (saline)).	1	43	very low	study limitations (2 levels), imprecision (1 level)
BM-MSC vs. exercise	No difference on VAS between both groups: 3 month change score -8 (exercise) and -12.5 (MSC). (p=0.40)	1	48	very low	study limitations (2 levels), imprecision (1 level)
BM-MSC vs. PRP	VAS after 1 year improved mean 1.8 points in MSC group and mean 0.5 points in PRP group.	1	50	very low	study limitations (2 levels), imprecision (2 levels)
AD-MSC vs. PRP	Mean improvement of 34.1 points on VAS (0-100) 2 years after MSC therapy and 29.2 points in PRP group (p<0.001).	1	44	very low	study limitations (1 level), imprecision (2 levels)
AD-MSC vs. saline	Mean improvement of 3.4 points on VAS (0-10) 6 months after MSC therapy and no change in saline group.	1	24	low	imprecision (2 levels)
AD-MSC vs. exercise	Mean improvement of 4.1-4.2 points on VAS (0-10) 12 months after MSC therapy. No changes in the exercise group.	1	30	very low	study limitations (1 level), imprecision (2 levels)

AD-MSC v. HA	Improvement of (respectively left and right knees) 4.29-4.40 points on VAS (0-10) 12 months after MSC therapy and 2.78-2.83 points in the HA group (p=0.0190 left knees and p=0.0178 right knees).	1	53	very low	study limitations (1 level), imprecision (2 levels)
	<u>MRI outcomes</u>				
BM- MSC vs. HA	Improvement of cartilage quality and volume (MOCART, WORMS) 1 year after MSC therapy and no change after HA therapy.	2	86	low[22] very low[30]	study limitations (1 level, Wong et al.), inconsistency (1 level), imprecision (1 level)
BM-MSC vs. PRP	No change after 1 year on MRI following the WORMS protocol in both groups.	1	50	very low	study limitations (1 level), imprecision (2 levels)
AD-MSC vs. saline	No difference in cartilage defect size 6 months after MSC therapy and increase of cartilage defect size in saline group.	1	24	very low	inconsistency (1 level), imprecision (2 levels)
AD-MSC vs. exercise	Based on the 'articular cartilage pathology' subscale of the MOAKS, in the control group 33% of patients had no change after 12 months. In the intervention groups, no change of cartilage was scored in 70-78% and cartilage improvement in 0-11% of patients (one and two injections respectively).	1	30	very low	study limitations (1 level), imprecision (2 levels)
AD-MSC v. HA	Improvement of cartilage volume of 108 ± 220 mm^3 (right knees) to 193 ± 282 mm^3 (left knees) 12 months after MSC therapy and no significant change in the HA group.	1	53	very low	study limitations (1 level), inconsistency

					(1 level), imprecision (2 levels)

Table 2: GRADE assessment. BM-MSC = bone marrow-derived mesenchymal stem cells; AD-MSC = adipose tissue-derived mesenchymal stem cells, PB-MSC = peripheral blood-derived mesenchymal stem cells; HA = hyaluronic acid; PRP = platelet-rich plasma, MOCART = Magnetic Resonance Observation of Cartilage Repair Tissue, KOOS = Knee Injury and Osteoarthritis Outcome Score, VAS = visual analogue scale, WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index, WORMS = Whole-Organ Magnetic Resonance Imaging Score, KSS = Knee Society Score, MOAKS = MRI Osteoarthritis Knee Scores, LEAS = Lower Extremity Activity Scale, ns = not significant

First author	Year	Mean number of cells	Main outcomes	Timing of outcomes measured	Intervention final FU score	Control final FU score	Mean difference	95% CI	P-value**	Adverse events
Wong[30]	2013	1,46 ± 0,29 x 10^7	IKDC scores	6 mo, 1 y, 2 y	NA	NA	7.65	3.04 to 12.26	0.001 I	no serious adverse events
			Tegner score				0.64	0.10 to 1.19	0.021 I	
			Lysholm score				7.61	1.44 to 13.79	0.016 I	
			MOCART scoring system	1 y			19.6	10.5 to 28.6	< 0.001	
Koh[31]	2014	4,11 x 10^6	KOOS pain	last follow-up (mean 24.4 mo)	81.2 ± 6.9	74.0 ± 5.7	7.20*	3.76 to 10.64*	< 0.001 I	adverse events not reported
			KOOS symptom		82.8 ± 7.2	75.4 ± 8.5	7.40*	3.12 to 11.68*	0.006 I	
			KOOS sport and recreation		NA	NA	NA	NA	NA	
			KOOS ADL							
			KOOS QOL							
			VAS pain (100 mm scale)		10.2 ± 5.7	16.2 ± 4.6	-6.00*	-8.82 to -3.18*	< 0.001 I	

			Lysholm score		84.7 ± 16.2	80.6 ± 13.5	4.10*	-4.01 to 12.21*	0.357	
Lamo-Espinosa[22, 44]	2016 and 2018	10 x 10^6 (low-dose) or 100 x 10^6 (high-dose)	VAS joint pain	12 mo	int. low-dose median 2 (IQR 1 to 3)	median 4 (IQR 3 to 5)	NA	NA	NA	12 mo: articular pain requiring anti-inflammatory treatment during the first 24 h after infiltration (int. high-dose 6, int. low-dose 3, control 1) 48 mo: no serious adverse events or complications
					int. high-dose median 2 (IQR 0 to 4)				NA	
				48 mo	int. low-dose median 2 (IQR 2 to 5),	median 7 (IQR 6 to 7)			0.01	
					int. high-dose median 3 (IQR 3 to 4)				0.004 l	
			Likert version of the WOMAC pain	12 mo	int. low-dose median 3.5 (IQR 3 to 5)	median 2 (IQR 1 to 6)			NA	
					int. high-dose median 2.5 (IQR 2 to 4)				NA	
			Likert version of the	12 mo	int. low-dose median 2 (IQR 1 to 2),	median 2 (IQR 1 to 2)			NA	

			WOMAC stiffness		int. high-dose median 2 (IQR 1 to 2)				NA	
			Likert version of the WOMAC physical function	12 mo	Int. low-dose median 17 (IQR 10 to 20)	median 9.5 (IQR 5 to 23)			NA	
					int. high-dose median 11 (IQR 9 to 14)				NA	
			Likert version of the WOMAC overall	12 mo	int. low-dose median 21.5 (IQR 15 to 26)	median 13.5 (IQR 8 to 33)			NA	
					int. high-dose median 16.5 (IQR 12 to 19)				NA	
				48 mo	int. low-dose median 17 (IQR 13 to 25.5)	median 27 (IQR 17 to 30)			0.04 I	
					int high-dose median 16.5 (IQR 8 to 23)					

			WORMS score	12 mo	int. low-dose median 90 (IQR 67 to 140)	median 83 (IQR 25 to 95)	NA	NA	NA	
					int. high-dose median 53 (IQR 46 to 82)					
Goncars[32]	2017	38.64 ± 33.7 x 10^6 (range 8.3 to 158.97 x 10^6)	KOOS pain	12 mo	79.53	61.55	NA	NA	<0.05 I	no adverse events
			KOOS symptom		NA	NA	NA	NA	ns	
			KOOS sport and recreation							
			KOOS ADL							
			KOOS QOL							
			KOOS global score							
			KSS							
			KSS function							
Turajane[33]	2017	with GFA: 1143, 1264, 1276 x 10^3 per 3 ml, without GFA: 1095, 1252, 1253 x 10^3 per 3	WOMAC pain	12 mo	with GFA: 28, without GFA: 30	57	NA	NA	int. with GFA vs. control 0.003 I, int. without GFA vs. control	no notable adverse events

		ml (1st, 2nd and 3rd resp.)							0.003 l, int. pooled vs. control 0.004 l	
			WOMAC stiffness		with GFA: 9, without GFA: 20	31.5			int. with GFA vs. control 0.0001 l, int. without GFA vs. control 0.053, int. pooled vs. control 0.0001 l	
			WOMAC physical function		with GFA: 15, without GFA: 25	38.8			int. with GFA vs. control 0.001 l, int. without GFA vs. control 0.003 l, int. pooled vs. control 0.001 l	
			WOMAC overall		with GFA: 52, without GFA: 75	126.8			int. with GFA vs. control < 0.001 l, int. without	

									GFA vs. control < 0.001 I, int. pooled vs. control < 0.001 I	
Emadedin[34]	2018	40 x 10^6	VAS	6 mo	NA	NA	NA	NA	0.65	22 AE (all grade 1-3, no serious AEs)
			WOMAC total		NA				0.01 I	
			WOMAC pain		mean 13.1 ± 18.1				0.001 I	
			WOMAC stiffness		NA				0.40	
			WOMAC function						0.04 I	
			MCII pain						0.44	
			MCII function						0.18	
			PASS pain						0.46	
			PASS function						0.06	
Centeno[35]	2018	NA	VAS	3 mo	2.7 (SD 2.1)[#]	3.8 (SD 2)[#]	-1.10*	-2.29 to 0.09*	0.40	no serious adverse events reported; 16 patients reported
			LEAS		13.5 (SD 2.2) [#]	11.6 (SD 2.8) [#]	1.90*	0.44 to 3.36*	0.002 I	

			KSS knee score		87.7 (SD 10.5)[#]	76.6 (SD 9.4)[#]	11.10*	5.28 to 16.92*	<0.001 l	knee pain after treatment
			KSS function score		91.9 (SD 12.4)[#]	85.5 (SD 11.8) [#]	6.40*	-1.42 to 14.22*	0.17	
			SF-12 physical		44.5 (SD 10.3) [#]	38.6 (SD 8.9) [#]	5.90*	0.35 to 11.45*	0.27	
			SF-12 mental		55.9 (SD 6.7) [#]	57.4 (SD 7.5) [#]	-1.50*	-5.62 to 2.62*	0.68	
			Knee range of motion		133.5 (SD 10.6) [#]	13.8 (SD 6.5) [#]	1.70*	-3.41 to 6.81*	NA	
Lee[36]	2018	1 x 10^8	WOMAC total	6 mo	26.7 ± 13.3	NA	NA	NA	NA	int: 10 (83 %) patients; control: 7 (58 %). All grade 1-3.
			WOMAC pain		NA					
			WOMAC stiffness							
			WOMAC function							
			VAS pain		3.4 ± 1.5					
			KOOS pain		NA					
			KOOS symptom							
			KOOS ADL							
			KOOS sport							

			KOOS QOL							
			MRI size of cartilage defect		314.86 mm² ± 267.33	355.61 mm² ± 258.54	-40.75*	-251 to 169*	0.0051 I	
Bastos[25]	2020	40 x 10^6	KOOS global	12 mo	MSC: mean 54.2 ± 24.7	mean 54.4 ± 22.7	-0.20*	-16.41 to 16.01*	NA	adverse events not reported
					MSC+PRP: mean 59.9 ± 24.8		5.50*	-11.39 to 22.39*		
					MSC vs. MSC+PRP		-5.70*	-23.45 to 12.05*		
			KOOS symptom	12 mo	MSC: mean 61.6 ± 22.5	mean 56.1 ± 22.3	5.50*	-9.76 to 20.76*		
					MSC+PRP: mean 60.5 ± 17.6		4.40*	-9.65 to 18.45*		
					MSC vs. MSC+PRP		1.10*	-13.27 to 15.47*		
			KOOS pain	12 mo	MSC: mean 56.8 ± 26.5	mean 59.5 ± 22.2	-2.70*	-19.43 to 14.03*		

					MSC+PRP: mean 65.5 ± 26.3		6.00*	-11.35 to 23.35*		
					MSC vs. MSC+PRP		-8.70*	-27.63 to 10.23*		
			KOOS function	12 mo	MSC: mean 58.4 ± 27.5,	mean 61.6 ± 24.4	-3.20*	-20.98 to 14.58*		
					MSC+PRP: mean 66.3 ± 27.4		4.70*	-13.75 to 23.15*		
					MSC vs. MSC+PRP		-7.90*	-27.59 to 11.79*		
			KOOS sport	12 mo	MSC: mean 36.6 ± 29.5	mean 36.2 ± 29.5	0.40*	-19.74 to 20.54*		
					MSC+PRP: mean 47.1 ± 34.5		10.90*	-11.97 to 33.77*		
					MSC vs. MSC+PRP		-10.50*	-33.01 to 12.01*		
			KOOS QOL	12 mo	MSC: mean 40.2 ± 25.9	mean 32.0 ± 29.3	8.20*	-10.64 to 27.04*		
					MSC+PRP: mean 35.7 ± 25.6		3.70*	-15.63 to 23.03*		
					MSC vs. MSC+PRP		4.50*	-13.96 to 22.96*		

Freitag[37]	2019	100 x 10^6	NPRS	12 mo	int 1 injection: mean 2.6 (SD 1.8)	mean 6.1 (SD 2.6)	-3.50*	-5.46 to -1.54*	.00 l	no serious adverse events. Int 1 injection group 6 (60%) patients had mild AE and in 2 injections group 50% had mild AE after first injection and 40% after second injection.
					int 2 injections: mean 2.3 (SD 2)		-3.80*	-5.83 to -1.77*	.00 l	
					1 vs 2 injections		0.30*	-1.37 to 1.97*	ns	
			KOOS pain		int 1 injection: mean 77.3 (SD 11.3)	mean 48.9 (SD 12.7)	28.40*	17.86 to 38.94*	.03 l	
					int 2 injections: mean 80.5 (SD 10.7)		31.60*	21.31 to 41.89*	.02 l	
					1 vs 2 injections		-3.20*	-12.85 to 6.45*	ns	
			KOOS symptom		int 1 injection: mean 82.6 (SD 14.1)	mean 47.9 (SD 13.6)	34.70*	22.56 to 46.84*	.00 l	
					int 2 injections:		30.20*	18.41 to 41.99*	.00 l	

					mean 78.1 (SD 13.3)					
					1 vs 2 injections		4.50*	-7.51 to 16.51*	ns	
			KOOS ADL		int 1 injection: mean 84.3 (SD 9.4)	mean 60.7 (SD 13.5)	23.60*	14.23 to 32.97*	.025 l	
					int 2 injections: mean 88.8 (SD 8.4)		28.10*	18.25 to 37.95*	.017 l	
					1 vs 2 injections		-4.50*	-12.31 to 3.31*	ns	
			KOOS sport		int 1 injection: mean 67.8 (SD 17.5)	mean 31.5 (SD 33)	36.30*	13.15 to 59.45*	.00 l	
					int 2 injections: mean SD 70 (SD 17.8)		38.50*	15.26 to 61.74*	.00 l	
					1 vs 2 injections		-2.20*	-17.67 to 13.27*	ns	
			KOOS QOL		int 1 injection: mean 61.8 (SD 13)	mean 33.9 (SD 18.9)	27.90*	13.68 to 42.12*	.003 l	

					int 2 injections: mean 56.3 (SD 18)		22.40*	6.22 to 38.58*	.006 l	
					1 vs 2 injections		5.50*	-8.26 to 19.26*	ns	
			WOMAC		int 1 injection: mean 84 (SD 9.4)	mean 59.1 (SD 12.8)	24.90*	15.06 to 34.74*	.00 l	
					int 2 injections: 87.3 (SD 8)		28.20*	18.84 to 37.56*	.00 l	
					1 vs 2 injections		-3.30*	-10.95 to 4.35*	ns	
			MOAKS		NA	NA	NA	NA	NA	
Lu[26]	2019	5 x 10^7	WOMAC	12 mo	21.35 ± 18.19	27.25 ± 16.33	-5.90*	-15.30 to 3.50*	NA	int. 19 patients (73.07%) mild to moderate adverse events, 0 severe adverse events. Control 14 patients (53.85%) mild to moderate adverse events. 1 (3.8%) severe adverse event (infection) (in control group).
			VAS		NA	NA	NA	NA	< 0.05 l	
			SF-36		71.96 ± 12.79	83.13 ± 15.59	-11.17*	-18.92 to -3.42*	0.0097 l	
			MRI cartilage repair		NA	NA	NA	NA	NA	

Lamo-Espinosa[38]	2020	100x10^6	VAS	12 mo	3.5 ± 2.5	4.5 ± 2.2	NA	NA	NA	articular pain during the first 24 h after infiltration (int. 6, control 0). No serious adverse events or complications.
			WOMAC pain		4.1 ± 3.6	4.5 ± 3.2	NA	NA	NA	
			WOMAC stiffness		2.1 ± 1.9	2.1 ± 1.6	NA	NA	NA	
			WOMAC physical function		16.7 ± 11.6	15.5 ± 11.9	NA	NA	NA	
			WOMAC total		23.0 ± 16.6	22.3 ± 15.8	NA	NA	NA	
			knee joint space on X-ray		median 1.41 mm (IQR 1.96)	median 1.77 mm (IQR 1.97)	NA	NA	NA	
			WORMS (MRI)		median 79.8 (SD 29.1)	median 77.5 (SD 31.5)	NA	NA	NA	
Kim[39]	2020	4,7x10^6	Lysholm score	mean 27.6 mo (range 24-36 mo)	MSC+ allogenic cartilage mean 89.3 (SD 16.1)	MSC: mean 85.4 (SD 15.9)	NA	NA	0.002 I	No major adverse events
			KOOS pain		MSC+allogenic cartilage mean 75.6 (SD 12.8)	MSC: mean 70.4 (SD 13.2)	NA	NA	0.041 I	

			KOOS symptom		MSC+allogenic cartilage mean 73.6 (SD 17.8)	MSC: mean 67.3 (SD 17.2)	NA	NA	< 0.001 I	
			KOOS activities of daily life		MSC+allogenic cartilage mean 76.2 (SD 17.2)	MSC: mean 70.3 (SD 16.7)	NA	NA	0.0017 I	
			KOOS sports and recreation		MSC+allogenic cartilage mean 53.2 (SD 22.1)	MSC: mean 48.6 (SD 18.8)	NA	NA	< 0.001 I	
			KOOS quality of life		MSC+allogenic cartilage mean 62.3 (SD 23.1)	MSC: mean 52.1 (SD 20.3)	NA	NA	0.009 I	
Anz[40]	2020	NA	IKDC score	12 mo	mean 64.3 (SD 20.8)	mean 63.7 (SD 19.6)	NA	NA	NA	Not reported
			WOMAC total		mean 19.4 (SD 16.2)	mean 16.8 (SD 16.9)	NA	NA	NA	

			WOMAC pain		mean 3.5 (SD 3.1)	mean 2.9 (SD 3.1)	NA	NA	NA	
			WOMAC stiffness		mean 2.3 (SD 1.6)	mean 1.8 (SD 1.5)	NA	NA	NA	
			WOMAC function		mean 12.8 (SD 11.6)	mean 11.3 (SD 12.2)	NA	NA	NA	

Table 3: study outcomes. NA= not applicable, ns= not significant, mo= months, y = years, FU = follow-up, MSC = mesenchymal stem cells, PRP = platelet-rich plasma, NPRS = numeric pain rating scale, MOAKS = MRI Osteoarthritis Knee Scores, CI = confident interval, IKDC = International Knee Documentation Committee, MOCART = Magnetic Resonance Observation of Cartilage Repair Tissue, KOOS = Knee Injury and Osteoarthritis Outcome Score, ADL = activities of daily living, QOL = quality of life, VAS = visual analogue scale, IQR = interquartile range, WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index, WORMS = Whole-Organ Magnetic Resonance Imaging Score, KSS = Knee Society Score, GFA = growth factor addition, MCII = Minimum Clinically Important Improvement, PASS = Patient Acceptable Symptom State, LEAS = Lower Extremity Activity Scale, SF-12 = Short Form-12 scales, SF-36 = Short Form-36 scales, CFU = colony forming units.

* Calculated using RevMan V5.4.1; *Review Manager (RevMan) [Computer program]. Version 5.4, The Cochrane Collaboration, 2020.*

** I indicates the intervention group showed significant improvement compared with controls, while C indicates the control group showed significant improvements compared to the intervention group

obtained from trial authors