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Methodological flaws in meta-analyses of clinical studies on the management of knee osteoarthritis with stem cells: a systematic review

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Background: Conclusions of meta-analyses of clinical studies may substantially influence opinions of perspective patients and stakeholders in health care. Nineteen meta-analyses of clinical studies on the management of primary knee osteoarthritis (pkOA) with stem cells, published between January 2020 and July 2021, came to inconsistent conclusions regarding the efficacy of this treatment modality. It is possible that a separate meta-analysis based on an independent, systematic assessment of clinical studies on the management of pkOA with stem cells may reach a different conclusion.
Methods: PubMed, Web of Science and the Cochrane library were systematically searched for clinical studies and meta-analyses of clinical studies on the management of pkOA with stem cells. All clinical studies and meta-analyses identified were evaluated in detail, as were all sub-analyses included in the meta-analyses.
Results: The inconsistent conclusions regarding the efficacy of treating pkOA with stem cells in the 19 assessed meta-analyses were most probably based on substantial differences in literature search strategies among different authors, misconceptions about meta-analyses themselves, and misconceptions about the biology of stem cells. An independent, systematic review of the literature yielded a total of 183 studies, of which 33 were randomized clinical trials, including a total of 6860 patients with pkOA. However, it was not possible to perform a scientifically sound meta-analysis.
Conclusion: Clinicians should interpret the results of the 19 assessed meta-analyses of clinical studies on the management of pkOA with stem cells with caution, and should be cautious of the conclusions drawn therein. Clinicians and researchers should strive to participate in FDA and/or EMA reviewed and approved clinical trials to provide clinically and statistically valid efficacy.

Keywords: meta-analyses; primary knee osteoarthritis; stem cells; systematic review

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Conclusion: Clinicians should interpret the results of the 19 assessed meta-analyses of clinical studies on the management of pkOA with stem cells with caution, and should be cautious of the conclusions drawn therein. Clinicians and researchers should strive to participate in FDA and/or EMA reviewed and approved clinical trials to provide clinically and statistically valid efficacy.

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1. Introduction

Osteoarthritis (OA) is the most common cause of pain and disability worldwide, especially in the elderly population.[1-3] The hip and knee joints are mostly commonly affected, and women are more frequently affected than men.[4,5] There is no cure for OA despite its high prevalence and deleterious impact on the quality of life of affected individuals.[1,3] The currently available therapeutic measures aim to relieve pain and maximize functional capacity and quality of life, while minimizing adverse effects from drugs and invasive interventions.[6] Patients suffering from primary knee OA (pkOA) often report refractory, severe and disabling pain, and are eventually referred for partial or total arthroplasty.[7,8]

Intra-articular (i.a.) injection of platelet rich plasma (PRP), corticosteroid (CS) and hyaluronic acid (HA) are commonly used to manage pkOA.[9-11] These injections can easily be administered, fewer treatment sessions are necessary compared with other treatments, and treatment adherence of patients is relatively easy to achieve (except for repeated injections). According to the Osteoarthritis Research Society International (OARSI) guidelines, i.a. injection of CS and HA (but not of PRP) are among the recommended treatments for pkOA, dependent upon comorbidity status.[12] A recent meta-analysis of the efficacy and safety of i.a. injection of CS and HA for pkOA concluded that both therapies are relatively safe and lead to comparable improvement of knee function.[13] According to such meta-analysis, better short-term effects (up to 1 month) are obtained with CS than with HA, and better long-term effects (up to 6 months) with HA than with CS.[13] On the other hand, i.a. injection of HA causes more topical adverse effects than i.a. injection of CS.[13]

During the last 2 decades, various studies proposed the management of pkOA with different types of stem cells. By means of a systematic literature search in PubMed, Web of Science and the Cochrane database according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines[14], we identified 19 meta-analyses, all published between January 2020 and July 2021.[15-33] Unfortunately, the conclusions of these meta-analyes are inconsistent. Specifically, these meta-analyses demonstrated (i) efficacy of treating pkOA with stem cells;[16,18,19,23,28,30] (ii) superiority of autologous stem cells derived from adipose tissue over other types of stem cells in the management of pkOA;[15,20,22,27,32] (iii) efficacy of treating pkOA with autologous, adipose-derived stem cells, without comparison with other types of stem cells;[21,33] (iv) superiority of autologous, bone marrow-derived stem cells over autologous, adipose-derived stem cells in the management of pkOA;[31] (v) efficacy of treating pkOA with autologous, bone marrow-derived stem cells, without comparison with other types of stem cells;[17] (vi) efficacy of treating pkOA with allogeneic stem cells;[25] (vii) efficacy of treating pkOA with stem cells only in conjunction with surgery;[29] and (viii) lack of efficacy of treating pkOA with stem cells[24,26] (Table S1) (Tables S1-S22 are provided in the Online Supplementary Material).

To determine the reasons for these inconsistent conclusions, we performed a comprehensive assessment of all clinical studies included in these 19 meta-analyses.[15-33] Furthermore, we determined whether a separate meta-analysis based on an independent, systematic assessment of studies on the management of pkOA with stem cells would reach a different conclusion.

2. Methods

2.1. Literature search

PubMed, Web of Science and the Cochrane library were searched for "knee osteoarthritis stem cell*", "knee osteoarthritis stromal vascular fraction" and "knee osteoarthritis SVF" from the days of inception of these databases until August 07, 2021 according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)14 guidelines. Duplicates were excluded. This search strategy found many more clinical studies than evaluated in the 19 assessed meta-analyses.[15-33]

2.2. Assessment of published meta-analyses

The stratetgy of the first assessment of the identified publications is summarized in Figure 1. In a first step, for each identified publication it was determined by reading title and abstract whether it represented a meta-analysis of clinical studies on the management of pkOA with stem cells and was published in 2020 or 2021. This was independently undertaken by CS and CA. Results were compared and discussed until agreement was achieved. Afterwards, all studies included in the identified meta-analyses that reported the management of pkOA with stem cells were classified with regard to the type of study as summarized in Tables S2 and S3, as well as with regard to the type of stem cells used as summarized in Table S4. Thereafter, all identified meta-analyses were classified by CS and CA with regard to the type of meta-analysis performed as summarized in Table S5.

Then, 2 types of meta-analyses were excluded from further assessment: those in which only endpoints of the same patients before and after treatment were compared (four meta-analyses) (Class 2 in Table S5), and those in which the vast majority (>80%) of clinical studies included addressed management of pkOA with different modalities than stem cells (three meta-analyses) (Class 3 in Table S5).

Afterwards, the quality of each sub-analysis performed in the remaining 12 meta-analyses (Class 1 in Table S5) was assessed by CS and CA according to the quality criteria outlined in Table 1.

2.2. Systematic assessment of clinical studies on treatment of primary knee osteoarthritis with stem cells

The stratetgy of the second assessment of the identified publications is summarized in Figure 2. In a first step, CS and CA excluded reviews and investigations that did not represent clinical studies on the management of pkOA with stem cells. Then, each study identified by this search was classified with regard to the type of study as summarized in Tables S2 and S3 and with regard to the type of stem cells used as summarized in Table S4. Furthermore, it was determined which analyses could be performed that fulfilled all quality criteria summarized in Table 1. All this was undertaken by CS and CA.

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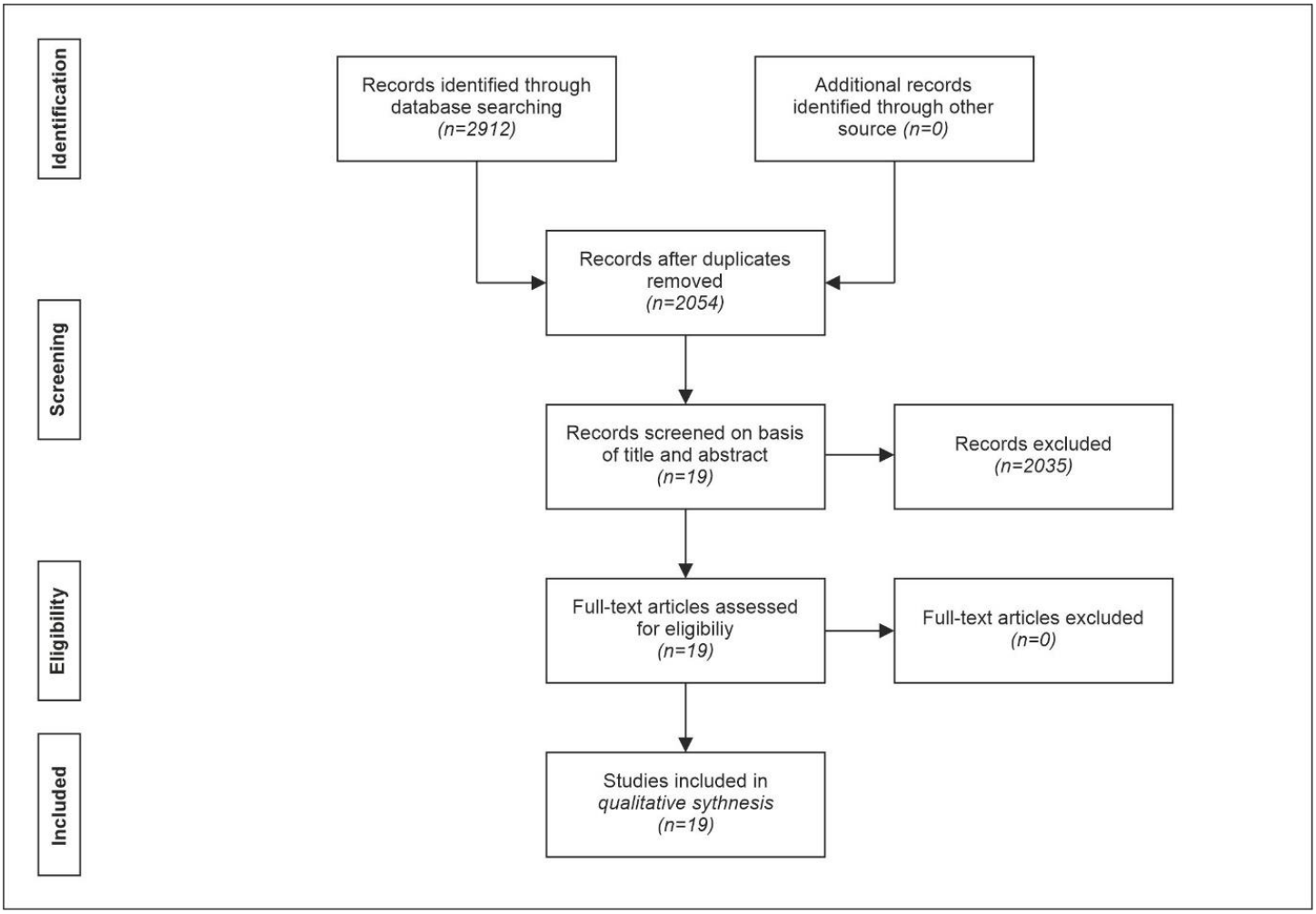

Figure 1 | Systematic review flow chart of the first literature search regarding meta-analyses of clinical studies on treatment of primary knee osteoarthritis with stem cells that were published between January 2020 and July 2021, performed according to the PRISMA guidelines[14] on 07 August 2021.

3. Results

3.1. Assessment of published meta-analyses

A total of 56 clinical studies[S1-S56] (note that References S1 to S56 are provided in the Supplement) were included in the 19 assessed meta-analyses; details of these 56 clinical studies are provided in Table S6. Classification of these 56 studies with regard to the type of study is summarized in Tables S2 and S3. Two of these 56 studies[S55,S56] (3.6%) could not be evaluated because they are not listed in PubMed, Web of Science and the Cochrane Library, and are not listed in Google Scholar.

Of note, 4 of the 54 studies[S1,S15,S38,S49] that could be evaluated (7.4%) did not address pkOA but, respectively, focal chondral, osteochondral, meniscal chondral or meniscal lesions. Furthermore, only 29 of the 54 studies that could be evaluated (53.7%) were randomized controlled trials (RCT); the other studies were RCTs with the contralateral knee as internal control (3/54=5.6%), prospective cohort studies (7/54=13.0%), retrospective cohort studies (2/54=3.7%), and case series without control group (13/54=24.1%) (Table S3).

Thirteen different types of stem cells (8 were autologous cell types and 5 were allogeneic cell types) were applied in the 54 studies that could be evaluated, (Table S4). The most frequently applied cell types were autologous, adipose-derived stem cells (ADSCs) (11/54=20.4%), autologous, bone marrow-derived mesenchymal stromal cells (BM-MSCS) (10/54=18.5%), autologous, adipose derived regenerative cells (ADRCs) (9/54=16.7%), and autologous bone marrow aspirate concentrate (BMAC) (7/54=13.0%). In 1 study[S6] no cells but allogeneic amniotic fluid was applied.

Each of the 19 assessed meta-analyses included an average number of 9.3 ± 4.6 (mean ± standard deviation) studies (median, 8; range, 2-18). Conversely, each study listed in Table S6 was included in an average of 3.1 ± 3.5 of the 19 assessed meta-analyses (median, 2; range, 1-15). Only 9 of the 56 studies (16.0%) were included in 5 or more of the 19 assessed meta-analyses, whereas 26 of the 56 studies (46.4%) were included in only 1 of the 19 assessed meta-analyses. None of the 56 studies were included in all assessed meta-analyses; the most frequently included study[S51] was an RCT in which injection of allogeneic BM-MSCs was compared with injection of HA (considered in 15 of the 19 assessed meta-analyses).

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Table 1 | Criteria used to assess the quality of sub-analyses in the meta-analyses summarized in Table S1 of studies in which treatment of primary knee osteoarthritis (pkOA) with different types of stem cells was investigated.

No.	Quality criterion	N	F [%]
1	At least 2 different clinical studies were included.	141	89.8
2	Only clinical studies on pkOA were included.	141	89.9
3	Only clinical studies in which stem cells were applied were included.	155	98.7
4	Only randomized controlled trials were included.	133	84.7
5	Only clinical studies were included in which application of stem cells was compared with placebo treatment, or in which application of stem cells plus concomitant therapy (including arthroscopic debridement, high tibial osteotomy, injection of hyaluronic acid, etc.) was compared with the concomitant therapy alone, respectively.	55	35.0
6	Only clinical studies using respectively autologous or allogeneic stem cells were included.	64	40.8
7	Only clinical studies in which respectively cultured or uncultured cells were applied were included.	133	84.7
8	Clinical studies in which more than 1 dose of stem cells were applied were only considered once in the corresponding meta-analysis.	100	63.4

Abbreviations: N_A and N_R = absolute (N_A) and relative (N_R) number of sub-analyses that fulfilled the corresponding criterion; No. = number.

In 4 of the 19 assessed meta-analyses[19,21,22,31], subjective (self-reported pain and function scores) and objective (cartilage measurements) endpoints of the same patients before and after treatment were analyzed. Since this approach cannot rule out the possibility that all reported and measured effects were based on the placebo effect in the management of pkOA[34-36], these meta-analyses were excluded from further assessment.

In the 3 network meta-analyses, respectively only two[26], three[23] and six[33] studies on the management of pkOA with stem cells were included, but respectively 41[26], 22[23] and 37[33] studies addressing the management of pkOA without injection of stem cells were included. Since this approach does not at all reflect the actually available literature on the management of pkOA with stem cells (c.f. Table S6), these network meta-analyses were also excluded from further assessment.

In the remaining 12 meta-analyses [15-18,20,24,25,27-30,32], a total of 157 sub-analyses were performed; details of these 157 sub-analyses and individual assessment according to the quality criteria listed in Table 1 are provided in Tables S7-S18. The absolute and relative numbers of sub-analyses that fulfilled respectively 0 / 1 / 2 / 3 / 4 / 5 / 6 / 7 / 8 of the quality criteria outlined in Table 1 were 0 / 0 / 2 / 3 / 9 / 18 / 94 / 30 / 1 (or 0% / 0% / 1.3% / 1.9% / 5.7% / 11.5% / 59.9% / 19.1% / 0.6%, respectively).

The 2 sub-analyses which fulfilled only 2 of the 8 quality criteria outlined in Table 1 are listed in Table S10, and compared the following studies with respect to the VAS pain score at 3 months and 6 months post treatment: a study in which the management of pkOA was performed using allogeneic amniotic fluid[S6], a RCT in which application of allogeneic ADSCs was compared with placebo treatment[S26] (study considered 2 times because of 2 different doses of stem cells), a RCT in which application of autologous BM-MSCs plus HA injection was compared to HA injection alone[S27] (study also considered 2 times because of 2 different doses of stem cells), and a study in which application of autologous BMC plus platelet poor plasma injection was compared with placebo treatment, with the contralateral knee as internal control[S41].

The only sub-analysis fulfilling all quality criteria outlined in Table 1 is listed in Table S15, and compared the following studies with respect to categorical data (worse/not worse) of different MRI evaluations, which were categorical structures with different scales and, thus, converted to categorical data by the authors of this meta-analysis[17]: a RCT in which the management of pkOA with allogeneic placental mesenchymal stem cells was compared with placebo treatment[S21], and a RCT in which the management of pkOA with allogeneic ADSCs was also compared with placebo treatment[S26].

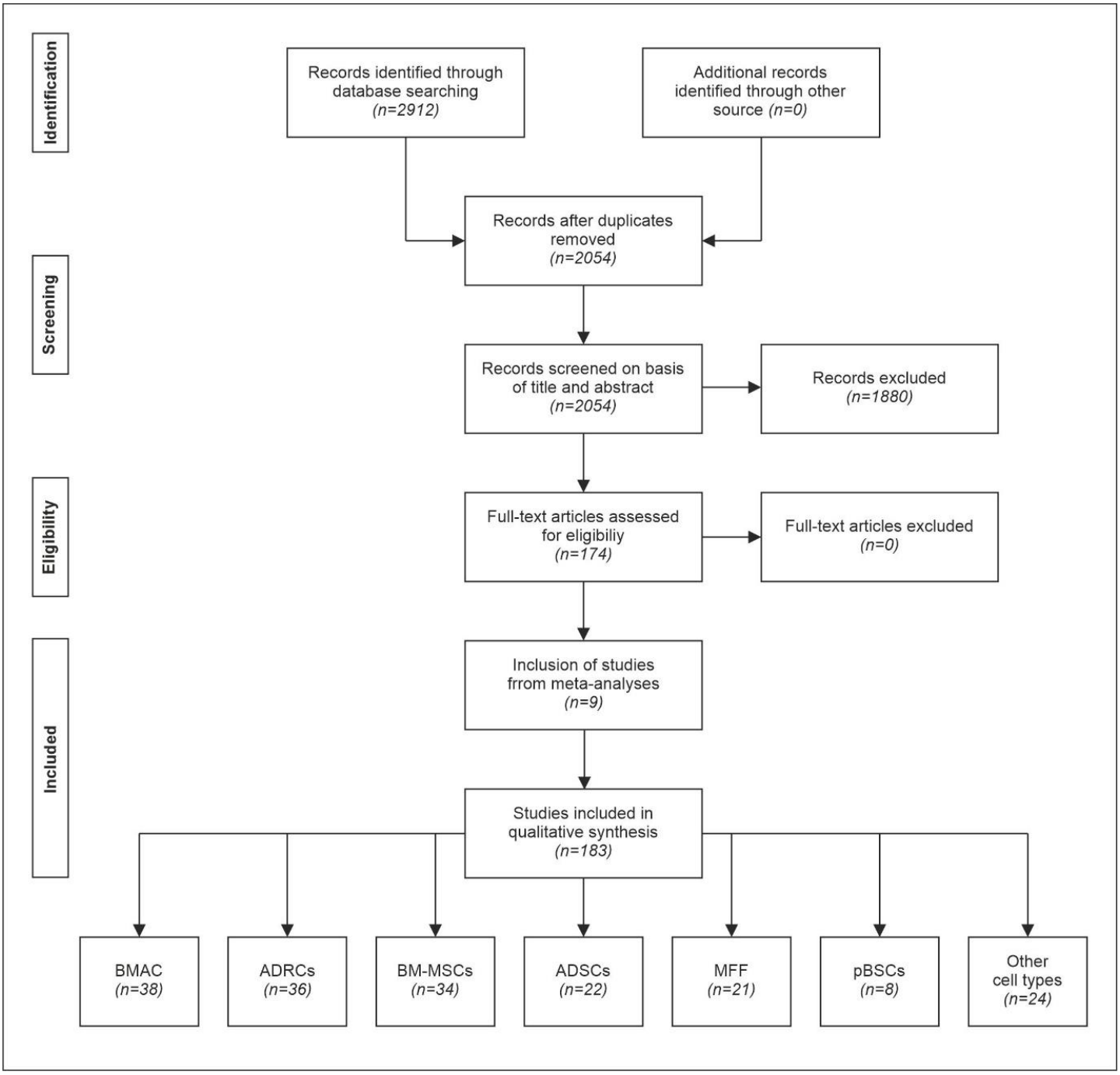

Figure 2 | Systematic review flow chart of the second literature search regarding treatment of primary knee osteoarthritis with stem cells, performed according to the PRISMA guidelines[14] on 07 August 2021. ADRCs = adipose-derived regenerative cells; ADSCs = adipose derived stem cells; BMC = bone marrow concentrate; BM-MSCs = bone marrow-derived mesenchymal stem cells; hUCB-MSCs = human umbilical cord blood-derived MSCs**;** MFF = micro-fragmented fat (from liposuction).

3.2. Systematic assessment of clinical studies on treatment of primary knee osteoarthritis with stem cells

Our independent literature search yielded 2912 publications, of which 174 described clinical studies with a total number of n=7146 patients treated with different types of stem cells (treatment groups). The other 2738 publications were duplicates (n=858) or addressed topics other than the management of pkOA with stem cells (n=681), reviews of the literature (n=476), animal studies (n=329), *in vitro* studies (n=285), commentaries (n=35), combined animal and in vitro studies (n=26), conference abstracts (n=17), study protocols (n=11), animal studies on different topics (n=6), reviews on different topics (n=5), position statements (n=4), errata (n=3) and retraction notes (n=2). Eight of the studies listed in Table S1[S3,S7,S12,S22,S38,S46,S50,S56] were not found in this literature search, as well as 1 study[S173] that was mentioned but not used in the sub-analyses performed in 1 of the assessed meta-analyses[28]. In these 9 additional studies, a total number of

n=532 patients were treated with different types of stem cells (treatment groups). Accordingly, the combined literature search (all assessed meta-analyses and the literature search outlined in Figure 2) yielded a total of 183 studies, with a total number of n=7678 patients. Details of these 183 studies are provided in Table S19. Categorization of these studies with respect to treatment and control treatment is provided in Table S20, with respect to the type of study in Table S21 and with respect to the types of stem cells used in Table S22. Results of the corresponding combined three-step categorization are summarized in Table 2.

Most of the 183 studies listed in Table S19 were performed using autologous BMAC (38 studies comprising a total of 2905 patients, among them 2588 patients with pkOA), followed by autologous ADRCs (36 studies; 1608 patients; 1568 with pkOA), autologous BM-MSCs (34 studies; 468 patients; 385 patients with pkOA), autologous ADSCs (22 studies; 368 patients; 346 patients with pkOA), microfragmented fat from liposuction (MFF) (21 studies; 1489 patients with pkOA), peripheral blood-derived MSCs (8 studies; 183 patients with pkOA; 54 patients with pkOA) and other cell types (24 studies; 657 patients; 430 patients with pkOA). Of note, in none of these 183 studies a serious adverse event after application of stem cells was reported.

Management of pkOA with stem cells was performed on a total of n=6860 patients in 143 of the 183 studies (Categories I-V in Table 2 and Table S20). The remaining 40 clinical studies (including a total of 818 patients) addressed respectively focal chondral, osteochondral, meniscal chondral or meniscal lesions (Category VI in Table 2 and Table S20), pathologies which are not addressed in the present setting.

In 65 of these 143 clinical studies on the management of pkOA, treatment with stem cells was compared to sham treatment or another treatment (RCTs or prospective or retrospective two- or three-cohort studies, respectively) (Categories I-IV in Table 2 and Table S20). On the other hand, the management of pkOA with i.a. injection of stem cells as the sole treatment (not considering rehabilitation) was performed in only 38 of these 65 studies (Categories I-III in Table 2 and Table S20), and i.a. injection of respectively saline or sham treatment was only performed in 8 of these 38 studies (Category I in Table 2 and Table S20).

According to the quality criteria of meta-analyses of studies on the management of pkOA with stem cells outlined in Table 1, it would generally be possible to perform the sub-analyses shown in Table 3. However, MFF must not be confused with ADRCs[37,38], and there are substantial differences between cultured stem cells derived from various human tissues[39]. The latter argument also applies to the 56 studies included in the 19 assessed meta-analyses, which further diminishes the value of these meta-analyses as assessment of the management of pkOA with stem cells.

Furthermore, a meta-analysis requires that in all included studies the same type of data is reported (i.e., same assessment scores, same or very similar intervals between treatment and follow-up, and mean, standard deviation and number of patients in each group). As shown in Table 4, this was not achieved for the clinical studies on the management of pkOA with respectively autologous ADRCs, autologous ADSCs and autologous BM-MSCs listed in Table 3.

4. Discussion

Concerning the first quality criterion outlined in Table 1, it should be mentioned that a meta-analysis is a statistical analysis that combines the results of multiple scientific studies. Hence, calculating overall effects based on a single study should not be considered a meta-analysis. However, calculating overall effects based on a single study is exactly what was done in 5 of the 19 assessed meta-analyses[15,20,24,25,29] and 16 of the 157 (10.2%) sub-analyses listed in Tables S7-S18.

With respect to the second and third quality criteria outlined in Table 1, it appears obvious that, in meta-analyses of studies in which the management of pkOA with stem cells was investigated, only studies focusing on the management of pkOA and applying stem cells should be included. However, this was not always the case in the 19 assessed meta-analyses. The pathomechanisms of focal chondral, osteochondral or meniscal chondral lesions[S1,S15,S38] as well as of injuries that require partial medial meniscectomy[S49] are not the same as the pathomechanisms of pkOA. This will likely impact on treatment outcome when applying stem cells. Furthermore, despite the fact that stem cells can be isolated from amniotic fluid[40], in our opinion injection of allogeneic amniotic fluid itself[S6] should not be considered a stem cell treatment, as it does not contain, by definition, stems cells, though it may contain products of secretion by stem cells.

Concerning the fourth quality criterion outlined in Table 1, non-randomized clinical trials and studies in which the contralateral knee was used as internal control may differ from RCTs in terms of selection bias (result of systematic differences between baseline characteristics of the groups that are compared[41]), performance bias (result of systematic differences between groups in the care that is provided, or in exposure to factors other than the interventions of interest[42]), and attrition bias (result of systematic differences between groups in withdrawals from a study[41]). Accordingly, non-randomized clinical trials and studies in which the contralateral knee was used as internal control should not be combined with RCTs in meta-analyses. However, this quality criterion was not fulfilled in 24 of the 157 (15.3%) sub-analyses performed in the 12 assessed meta-analyses (Category 1 in Table S5).

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Table 2 | Detailed analysis of clinical studies on the management of pkOA with stem cells (summarized in Table S19) that were identified during an evidence-based, systematic review of the literature according to the PRISMA guidelines[14] performed on August 07, 2021. The categories of studies (I to VI) are explained in Table S20, and the types of study (a to d) in Table S21.

Category	**I**				**II**				**III**				**IV**				**V**		***VI***						**N_{pkOA}**	***N_{CL}***
Type of study	**a**	**b**	**c**	**d**	**a**	**b**	**c**	**d**	**a**	**b**	**c**	**d**	**a**	**b**	**c**	**d**	**e**	**f**	***a***	***b***	***c***	***d***	***e***	***f***		
ADRCs	1							1			1	2	2	1	5	1	20	1	*1*						1568	*40*
ADSCs	2				1				4		5		1		1		3	1	*1*				*1*	*2*	346	*22*
MFF					1						2	1	1			1	15								1489	
CLL																	1								20	
BMA																	1								3	
BMAC		1			2				1	3			1	1		4	13		*1*		*3*	*1*	*6*	*1*	2588	*317*
BM-MSCs	1				1				1		1	1	7				11	2	*3*				*4*	*2*	385	*83*
Cs/CPs																							*1*	*1*		*13*
CSCs																							*1*			*15*
MACI																							*1*			*15*
S-MSCs																	1		*1*				*2*		8	*18*
Ch-TGFß	2																								128	
hUC-MSCs					2												1						*1*		75	*
hUCB-MSCs																	5		*1*				*1*		186	*166*
P-MSCs	1																								10	
pBSCs													1				3		*3*				*1*		54	*129*
Sum	**7**	**1**	**0**	**0**	**7**	**0**	**0**	**1**	**6**	**3**	**9**	**4**	**13**	**2**	**6**	**6**	**74**	**4**	***11***	***0***	***3***	***1***	***19***	***6***	**6860**	***818***

Abbreviations: ADRCs = adipose-derived regenerative cells; ADSCs = adipose-derived stem cells (obtained by culturing ADRCs); BMA = bone marrow aspirate; BMAC = bone marrow concentrate; BM-MSCs = bone marrow-derived mesenchymal stromal cells; CLL = centrifuged liposuction liquid; Cs = chondrocytes; CPs = chondrocyte precursors; CSCs = cartilage stem cells; hUC-MSCs = human umbilical cord-derived MSCs; hUCB-MSCs = human umbilical cord blood-derived MSCs; MACI = matrix-induced autologous chondrocyte implant; MFF = micro-fragmented fat (from liposuction); N_{CL} = number of patients with chondral lesions treated in these studies; N_{pkOA} = number of patients with pKOA treated in these studies; pBSCs = activated peripheral blood stem cells; P-MSCs = placental MSCs; S-MSCs = matrix-induced MSCs from synovia; * = number of patients not provided.

Table 3 | Sub-analyses that would generally be possible in a meta-analysis of studies on treatment of primary knee osteoarthritis with stem cells (summarized in Table S19) that were identified during an evidence-based, systematic review of the literature according to the PRISMA guidelines[14] performed on August 07, 2021.

R	Ca	T	First author	Y	Cell type	Treatment	Control
Autologous, uncultured cells							
S11	1	a	Garza	2020	ADRCs	C	RS
S25	4	a	Koh	2014	ADRCs	C + AD + HTO + PRP	AD + HTO + PRP
S149	4	a	Peretti	2018	MFF	C + AD	AD
Autologous, cultured cells							
S28	1	a	Lee	2019	ADSCs	C	Sa
S9	3	a	Freitag	2019	ADSCs	C	CM
S56	4	a	Zhang	2018	ADSCs	C + HA	C
S152	4	a	Qiao	2020	ADSCs	C + AD + MF + HA	MF or MF + HA
S8	1	a	Emadedin	2018	BM-MSCs	C	Sa
S50	4	a	Varma	2010	BM-MSCs	C + AD	AD
S53	4	a	Wong	2013	BM-MSCs	C + MF + HTO + HA	MF + HA + HTO
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA
S5	4	a	Bastos	2018	BM-MSCs	C + PRP	C
S128	4	a	Lamo-Espinosa	2018	BM-MSCs	C + HA	HA
S127	4	a	Lamo-Espinosa	2020	BM-MSCs	C + PRP	PRP
Allogeneic, cultured cells							
S7	1	a	Cherian	2015	Ch-TGFß	C	Sa
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA
S22	1	a	Kim	2018	Ch-TGFß	C	Sa
S26	1	a	Kuah	2018	ADSCs	C	Sa
S21	1	a	Khalifeh Soltani	2019	P-MSCs	C	Sa

Abbreviations: AD = arthroscopic debridement; ADRCs = adipose-derived regenerative cells; ADSCs = adipose-derived stem cells; BM-MSCs = bone marrow-derived mesenchymal stromal cells; C = cells; Ca = category of study as outlined in Table S20; Ch-TGFß = chondrocytes that overexpress transcription growth factor beta; HTO = high tibial osteotomy; MF = microfracture; MFF = micro-fragmented fat; P-MSCs = placental MSCs; PRP = platelet rich plasma; RS = Ringer solution; S = reference number (note that these references are provided in the Supplemental Online Material); Sa = saline; T = type of study as outlined in Table S21; Y = year of publication.

With respect to the fifth quality criterion outlined in Table 1, it is crucial to bear in mind that studies in which the management of pkOA with stem cells was compared to placebo treatment (or studies in which the management of pkOA with stem cells plus a concomitant therapy was compared to the concomitant therapy alone, respectively) must not be combined with studies in which the management of pkOA with stem cells (with or without concomitant therapy) was compared to a different treatment. However, this quality criterion was not fulfilled in 102 of the 157 (65.0%) sub-analyses performed in the 12 assessed meta-analyses. Specifically, in 86 of the 157 (54.8%) sub-analyses performed in the 12 assessed meta-analyses studies in which the management of pkOA with stem cells was compared with placebo treatment (or studies in which the management of pkOA with stem cells plus concomitant therapy was compared with the concomitant therapy alone, respectively) were combined with studies in which the management of pkOA with stem cells was compared with injection of HA. However, this approach disregards documented, positive effects of injection of HA as the management of pkOA[9-11] ,and may thus substantially underestimate the positive effects of treating pkOA with stem cells in meta-analyses. Furthermore, in 9 of the 157 (5.7%) sub-analyses performed in the 12 assessed meta-analyses, only studies in which the management of pkOA with stem cells was compared with the management of pkOA with injection of HA were included. Because of the documented, positive effects of injection of HA injection as the management of pkOA[9-11], these sub-analyses may reach a different conclusion than sub-analyses in which only studies were included in which the management of pkOA with stem cells was compared with placebo treatment (or studies in which the management of pkOA with stem cells plus concomitant therapy was compared with the concomitant therapy alone, respectively).

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Table 4 | Reported outcome in studies on treatment of primary knee osteoarthritis with respectively autologous, adipose-derived regenerative cells (ADRCs) or autologous, adipose-derived stem cells (ADSCs) listed in Table 3.

Table 4 (cont.)**R**	**FA**	**Reported outcome**
ADRCs		
S11	Garza	• WOMAC Total score at BL and at W6, M3, M6 and M12 (mean, median, interquartile range, median percentage range, minimum, maximum) • Cartilage loss (mean at BL, mean change at M6) • Outerbridge classification (median at BL, range at BL, median change at M6)
S25	Koh	• VAS pain score (mean and SD at baseline and at last follow-up) • KOOS subscores (mean improvement from BL to LFU) • Lysholm score (mean and SD at BL and LFU) • Weight-bearing line (%) (mean and SD at BL and LFU) • Femorotibial angle (°) (mean and SD at BL and LFU)
Autologous ADRCs		
S28	Lee	• VAS Pain score at BL, M3 and M6 (mean) • WOMAC Total and subscores at BL, M3 and M6 (mean) • KOOS subscores at BL, M3 and M6 (mean) • Size of cartilage defect in MRI at BL and M6 (mean, SD)
S9	Freitag	• VAS Pain score at BL, M1,5, M3, M6 and M12 (mean, 95% CI) • KOOS subscores at BL, M1,5, M3, M6 and M12 (mean, 95% CI) • WOMAC score at BL, M1,5, M3, M6 and M12 (mean, 95% CI)
S56	Zhang	• VAS Pain score at BL, M3, M6, M12, M24 and M36 (mean, SD) • WOMAC Total score at BL, M3, M6, M12, M24 and M36 (mean, SD)
S152	Qiao	• WOMAC Total and subscores at BL, M3, M6, M9, M12 and M24 (mean, SD) • SF-36 Physical Component and Mental Component subscores at BL, M3, M6, M9, M12 and M24 (mean, SD)
Autologous ADRCs		
S8	Emadedin	• Walking distance, painless walking distance, VAS Pain score, standing time, WOMAC total and subscores, time to gelling, flexion of knee, MCII Pain and Function scores, PASS Pain and Function scores (changes at M3 and M6 compared to BL; mean, range, standard error of difference, 95% CI of difference)
S50	Varma	• No access; this publication is not listed on the homepage of the Journal of the Indian Medical Association (https://www.ima-india.org/ima/left-side-bar.php?pid=347)
S53	Wong	• IKDC score, Lysholm score and Tegner score at BL and M6, M12 and M24 (mean, plotted individual data)
S27	Lamo-Espinosa	• VAS Pain score, WOMAC Total and subscores, range of motion, WORMS score at BL, M3, M6 and M12 (median, interquartile range)
S128	Lamo-Espinosa	• VAS Pain score, WOMAC Total score at BL, M3, M6, M12 and post-trial follow-up (median, interquartile range)
S127	Lamo-Espinosa	• VAS Pain score, WOMAC Total and subscores at 3, 6 and 12 months (mean, SD)

Abbreviations: BL = baseline; CI = confidence interval; FA = first author; LFU = last follow-up (range, M14-M24; mean: M19.8); M3 / M6 / M9 / M12 / M24 = 3 / 6 / 9 / 12 / 24 months post treatment; R = reference number (note that these references are provided in the Online Supplementary Material); SD = standard deviation; W6 = 6 weeks post treatment.

Concerning the sixth quality criterion outlined in Table 1, it is of note that, in contrast to autologous cells, application of allogeneic cells bears the risk of HLA mismatch; compromised clinical outcome after application of allogeneic cells was repeatedly reported in the literature.[43-45] In a position statement recently published by representatives of the U.S. Food and Drug Administration (FDA) in *The New England Journal of Medicine*[46], it was stated that autologous stem cells may typically raise fewer safety concerns than allogeneic stem cells. Consequently, studies using autologous stem cells should not be combined with studies using allogeneic stem cells in meta-analyses. However, this quality criterion was not fulfilled in 93 of the 157 (59.2%) sub-analyses performed in the 12 assessed meta-analyses.

With respect to the seventh quality criterion outlined in Table 1, ADSCs and BM-MSCs are expanded in culture before application, whereas ADRCs and BMAC are not. As a consequence, the percentage of certain cell types in ADSCs

fundamentally differs from the percentage of the same cell types in ADRCs[38], and the percentage of certain cell types in BM-MSCs fundamentally differs from the percentage of the same cell types in BMAC[47]. Hence, in meta-analyses of studies in which pkOA was treated with stem cells studies in which cultured cells were applied should not be combined with studies in which uncultured cells were applied. However, this quality criterion was not fulfilled in 24 of the 157 (15.3%) sub-analyses performed in the 12 assessed meta-analyses.

Concerning the eighth quality criterion outlined in Table 1, it should be realized that each study has its own inclusion and exclusion criteria which may vary among studies. Furthermore, there are many different ways to prepare a certain type of stem cells (e.g., approximately 40 different approaches to isolate ADRCs from adipose tissue are reported in the literature, with substantial inter-individual variations in the final cell suspensions[37]). Accordingly, considering the same study more than once in a meta-analysis can introduce bias (such as considering the 4 groups of patients treated in[S13] with 4 different doses of allogeneic BM-MSCs as 4 studies in a certain meta-analysis). However, this quality criterion was not fulfilled in 57 of the 157 (36.3%) sub-analyses performed in the 12 assessed meta-analyses.

We cannot offer any explanation why the 19 assessed meta-analyses did not adhere to the quality criteria summarized in Table 1. As outlined in detail above, these quality criteria reflect general considerations about meta-analyses and the very basic biology of stem cells.

4.1. Limitations

This review had two limitations. First, only PubMed, Web of Science and the Cochrane Library were searched. However, considering the sophisticated search strategies described in the 19 assessed meta-analyses and inclusion of all studies that were included in the 19 assessed meta-analyses also in the present investigation minimized the risk to overlook any relevant clinical study on the management of pkOA with stem cells. Second, no meta-analyses published before 2020 were assessed. However, this does not devalue our finding that the 19 meta-analyses published from January 2020 to July 2021 were not scientifically sound.

5. Conclusions

The inconsistent conclusions of the 19 assessed meta-analyses regarding the efficacy and safety of treating pkOA with stem cells were most probably based on substantial inter-individual differences in literature search strategies among different authors, misconceptions about meta-analyses themselves and misconceptions about the biology of stem cells. None of the 19 assessed meta-analyses should be considered to provide a scientifically definitive assessment of the efficacy of treating pkOA with stem cells. Accordingly, clinicians should be cautious of the 19 assessed meta-analyses of clinical studies on the management of pkOA with stem cells and the conclusions drawn therein, and strive to participate in FDA and/or EMA approved trials that have been reviewed to provide clinically and statistically valid efficacy.

Furthermore, at this time it appears impossible to perform a scientifically sound meta-analysis of such a heterogenous set of studies which investigated the management of pkOA with stem cells. There are strong indications that the management of pkOA with stem cells is safe and effective (e.g., all RCTs in Category I in Table S20 reported superiority of the management of pkOA over treatment with placebo). However, apparently it is still too early for scientifically sound meta-analyses on this topic.

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Authors' contributions

CS participated in conceptualization, development of methodology, formal analysis and investigation; managed resources, and performed data curation, writing of the original draft, visualization and project administration. CA participated in validation, formal analysis and investigation, as well as in reviewing and editing of the manuscript. DAP participated in validation as well as reviewing and editing of the manuscript. JPF and NM participated in reviewing and editing of the manuscript. EUA participated in conceptualization as well as reviewing and editing of the manuscript, and in project administration and supervision. All authors have read and approved the final version of the manuscript, and agree with the order of presentation of the authors.

Competing interests

C.S. is Advisory Medical Director of InGeneron, Inc. (Houston, TX). C.A. is Director of Medical and Scientific Affairs of InGeneron. E.U.A. is Executive Chair of InGeneron. InGeneron had no role in study design, data collection and analysis, interpretation of the data, and no role in the decision to publish and write this manuscript. No other potential conflicts of interest relevant to this article were reported.

Supplementary materials

Supplementary material associated with this article can be found at the end of this preprint.

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Methodological flaws in meta-analyses of clinical studies on treatment of knee osteoarthritis with stem cells

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Supplementary Material

Note: the reference numbers 15-33 refer to references in the main text, whereas the reference numbers S1-S187 refer to references provided in this Supplementary Material.

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Table S1 | Conclusions of 19 meta-analyses (published between January 2020 and July 2021) of studies in which treatment of primary knee osteoarthritis with different types of stem cells were investigated.

Abbreviations: AD = adipose-derived; BM = bone marrow-derived; BMAC = bone marrow aspirate concentrate; HA = hyaluronic acid; KOOS = Knee Injury and Osteoarthritis Outcome Score; MSCs = mesenchymal stem cells; OA = osteoarthritis; PRP = platelet rich plasma; R = reference number (note that the reference numbers provided in this table refer to the reference numbers in the main text); SVF = stromal vascular fraction; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

R	Conclusion (original quotes taken from the abstracts of the cited papers)
Meta-analyses that demonstrated efficacy of treating pkOA with stem cells	
15	"There are significant therapeutic effects on joint function, symptoms, and no permanent adverse effect has been found after stem cell treatment. It is promising to apply intro-articular injection of stem cells for OA to clinical application."
16	"Based on the current studies, our results suggested that MSCs were a promising option for the treatment of patients with knee OA."
17	"Intra-articular injection of MSCs is effective and safe to relieve pain and improve motor function of patients with knee OA in a short term which is different to conclusions of previous study."
18	"We demonstrated that MSC treatment could significantly decrease visual analog scale in a 12-month follow-up study compared with controls ($p < 0.001$). MSC therapy also showed significant decreases in WOMAC scores after the 6-month follow-up ($p < 0.001$). MSC therapy showed no difference compared with controls ($p > 0.05$) in adverse events. We suggest that MSC therapy could serve as an effective and safe therapy for clinical application in OA treatment."
19	"Stem cell therapy is certainly superior to traditional treatments in the conservative treatment of knee OA; it considerably reduces pain with no obvious additional side effects."
20	" MSCs relieve pain, stiffness, and dysfunction due to OA better than PRP, HA, and GCs and are not statistically correlated with greater safety concerns
Meta-analyses that demonstrated superiority of autologous, adipose-derived stem cells over other types of stem cells in treatment of knee OA	
21	"These findings suggested that MSCs are effective in the treatment of knee OA. AD-MSCs might be the most effective for relieving pain, and umbilical cord-derived mesenchymal stem cells might be the most effective for improving function. However, the current evidence does not support the use of MSCs for improving cartilage repair in knee OA patients."
22	"Overall, MSC-based cell therapy is a relatively safe treatment that holds great potential for OA, evidenced by a positive effect on pain and knee function. Using low-dose (25 million) and adipose-derived stem cells is likely to achieve better results."
23	"A single BMAC or SVF injection into the knee joint of patients with OA resulted in symptomatic improvement at short-term follow-up. However, SVF seemed to be more effective than did BMAC in the reduction of knee pain."
24	"Our analysis establishes the efficacy, safety, and superiority of AD-MSC transplantation, compared to BM-MSC, in the management of osteoarthritis of knee from available literature."
25	"The therapeutic effect of AD-MSCs on knee OA was more effective than that of BM-MSCs."

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Table S1 (cont.)

R	Conclusion
Meta-analysis that demonstrated efficacy of treating pkOA with autologous, adipose-derived stem cells, without comparison with other types of stem cells	
26	"Pooled analysis revealed that cell-based treatments definitively improve WOMAC scores, post treatment. These improvements increased with time. The studies in this meta-analysis have established the safety and efficacy of both AD-MSC therapy and SVF therapy for knee OA in old adults and show that they reduce pain and improve knee function in symptomatic knee OA suggesting that they may be effective therapies to improve mobility in an aging population."
27	"During 6 months of follow-up, AD-MSCs relieved pain the best; LP-PRP was most effective for functional improvement. During the 12-month follow-up, both AD-MSCs and LP-PRP showed potential clinical pain relief effects; functional improvement was achieved with LP-PRP."
Meta-analysis that demonstrated superiority of autologous, bone marrow-derived stem cells over autologous, adipose-derived stem cells in treatment of pkOA	
28	"Intra-articular injections of MSCs without any adjuvant therapies improves pain and function for osteoarthritis. Significantly better outcomes were obtained with the use of bone marrow MSCs as compared with adipose MSCs and with the use of cultured MSCs as opposed to uncultured MSCs."
Meta-analysis that demonstrated efficacy of treating pkOA with autologous, bone marrow-derived stem cells, without comparison with other types of stem cells	
29	"Intra-articular injection of culture-expanded MSCs without adjuvant surgery can improve pain for patients experiencing knee osteoarthritis at short-term follow-up (6-12 months)."
Meta-analysis that demonstrated efficacy of treating pkOA with allogeneic stem cells	
30	"Cell-based therapy had a better effect on KOOS improvement and pain relief without safety concerns. However, cell-based therapy did not show a benefit in terms of the WOMAC. Allogeneic cells might have advantages compared to controls in the WOMAC and KOOS scores."
Meta-analysis that demonstrated efficacy of treating pkOA with stem cells only in conjunction with surgery	
31	"The pooled standardized mean difference from meta-analyses showed statistically significant effects of MSC on self-reported physical function but not self-reported pain. MSCs provided functional benefit only in patients who underwent concomitant surgery."
Meta-analysis that demonstrated lack of efficacy of treating pkOA with stem cells	
32	"The ranking statistics like surface under the cumulative ranking curve values of our network meta-analysis support the use of steroids and HA for appropriate patients with knee OA. For pain relief and adverse events, steroids are most likely the best treatment, followed by HA. Single PRP, multiple PRP, and adipose MSC interventions do not result in a relevant reduction of joint pain nor improvement of joint function compared with placebo."
33	"Intra-articular MSC injection was not found to be superior to placebo in pain relief and functional improvement for patients with symptomatic knee OA."

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Table S2 | Categories of studies included in the 19 meta-analyses summarized in Table S1 of studies in which treatment of primary knee osteoarthritis (pkOA) with stem cells was investigated.

Abbreviations: Ca = category; CS = corticosteroid; HA = hyaluronic acid; i.a. = intra-articular; N_{all} = number of studies among all studies included in the 19 assessed meta-analyses; PRP = platelet rich plasma.

Ca	N_{all}	Description
I	8	Treatment of pkOA with i.a. injection of stem cells as the sole treatment (not considering rehabilitation), compared with i.a. injection of saline or sham treatment as control.
II	6	Treatment of pkOA with i.a. injection of stem cells as the sole treatment (not considering rehabilitation), compared with i.a. injection of respectively PRP, CS or HA as control.
III	10	Treatment of pkOA with i.a. injection of stem cells as the sole treatment (not considering rehabilitation), compared with other treatments than those in Categories I and II as control.
IV	12	Treatment of pkOA with combinations of stem cells and other modalities, compared with sham treatment or other treatments as control.
V	13	Treatment of pkOA with combinations of stem cells with or without other modalities, without control group (case series or case reports).
VI	4	Treatment of focal chondral, osteochondral or meniscal chondral lesions with stem cells as the sole treatment (not considering rehabilitation) or combinations of stem cells and other modalities, with or without other treatments as control.
VII	1	Treatment of pkOA without stem cells
N	2	Study not listed in PubMed, Embase, Web of Science, Cochrane Library and Googe Scholar
Sum	56	

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Table S3 | Types of studies included in the meta-analyses summarized in Table S1 of studies in which treatment of primary knee osteoarthritis (pkOA) with stem cells was investigated.

Abbreviations: Ca =category; N_{all} =number of studies among all studies included in the 19 assessed meta-analyses; N_{pkOA} = number of studies among those studies included in the 19 assessed meta-analyses that addressed pkOA.

Ca	N_{all}	N_{pkOA}	Description
a	29	25	Randomized controlled trials (RCTs)
b	3	3	RCTs with the contralateral knee as internal control
c	7	7	Prospective cohort studies
d	2	2	Retrospective cohort studies
e	13	13	Case series with more than one subject
f	0	0	Case reports with only one subject
N	2	2	Study not listed in PubMed, Embase, Web of Science, Cochrane Library and Googe Scholar
Sum	56	52	

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Table S4 | Cell types used in those studies included in the meta-analyses summarized in Table S1 in which treatment of primary knee osteoarthritis with stem cells was investigated.

Abbreviations: Auto = autologous cells; Allo = allogeneic cells; C = cells; N_{all} = number of studies among all studies included in the 19 assessed meta-analyses; N_{pkOA} = number of studies among those studies included in the 19 assessed meta-analyses that addressed pkOA.

Cell type	C	N_{all}	N_{pkOA}	Description
ADRCs	Auto	9	9	Autologous, adipose-derived regenerative cells
ADSCs	Auto	11	11	Autologous, adipose-derived stem cells (obtained by culturing ADRCs)
ADSCs	Allo	1	1	Allogeneic, adipose-derived stem cells
MFF	Auto	4	4	Autologous, micro-fragmented fat (from liposuction)
CLL	Auto	1	1	Autologous, centrifuged liposuction liquid
BMAC	Auto	7	7	Autologous bone marrow concentrate
BM-MSCs	Auto	10	9	Autologous, bone marrow-derived mesenchymal stem cells
BM-MSCs	Allo	3	2	Allogeneic, bone marrow-derived mesenchymal stromal cells
S-MSCs	Auto	1	0	Autologous, matrix-induced MSCs from synovia
Ch-TGFß	Allo	2	2	Allogeneic chondrocytes that overexpress transcription growth factor beta
hUC-MSCs	Allo	2	2	Allogeneic, human umbilical cord-derived MSCs
P-MSCs	Allo	1	1	Allogeneic, placental MSCs
pBSCs	Auto	1	0	Autologous, activated peripheral blood stem cells
No cells	Allo	1	1	Allogeneic amniotic fluid
Sum		54	50	

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Table S5 | Type of analysis performed in the meta-analyses summarized in Table S1 in which treatment of primary knee osteoarthritis with stem cells was investigated.

Abbreviation: Cl = Class; N = number of meta-analyses.

Cl	N	Description
1	12	Meta-analysis of studies in which treatment of pkOA with stem cells was compared with placebo treatment (or studies in which treatment of pkOA with stem cells plus concomitant therapy was compared with the concomitant therapy alone, respectively).
2	4	Meta-analysis in which only endpoints of the same patients before and after treatment were compared.
3	3	Network meta-analysis that included only a small number of studies on treatment of pkOA with stem cells and a much higher number of studies on treatment of pkOA without stem cells.
Sum	19	

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Table S6 | Details of the studies included in the meta-analyses summarized in Table S1 in which treatment of primary knee osteoarthritis (pkOA) with different types of stem cells was investigated.

Abbreviations: AD = arthroscopic debridement; BMC = bone marrow concentrate; C = cells; Ca = category of study as shown in Table S2; CM = conservative management; CS = corticosteroid; HA = hyaluronic acid; HTO = high tibial osteotomy; MACI = matrix-induced, autologous chondrocyte implant; MF = microfracture; N = number of meta-analyses in which the corresponding study was included; OA = oral acetaminophen; PPP = platelet poor plasma; PRP =platelet rich plasma; R = reference number; RS = Ringer solution; T = Type of study as shown in Table S3; U = unknown; x ADRCs = autologous, adipose-derived regenerative cells; x ADSCs = autologous, adipose-derived stem cells; x BMAC = autologous bone marrow aspirate concentrate; x BM-MSCs = autologous, bone marrow-derived mesenchymal stem cells; x CLL = autologous, centrifuged liposuction liquid; x MFF = autologous, micro-fragmented fat; x pBSCs = autologous, activated peripheral blood stem cells; y ADSCs = allogeneic, adipose-derived stem cells; y BM-MSCs = allogeneic, bone marrow-derived mesenchymal stromal cells; y Ch-TGFß = allogeneic chondrocytes that overexpress transcription growth factor beta; y hUC-MSCs = allogeneic, human umbilical cord-derived MSCs; y P-MSCs = allogeneic, placental MSCs; ● = study included in the corresponding meta-analysis.

								Reference no. in the main text																			
R	**Ca**	**T**	**First author**	**Year**	**Cells**	**T**	**Control**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**N**
S7	1	a	Cherian	2015	y Ch-TGFß	C	Saline																●				1
S13	1	a	Gupta	2016	y BM-MSCs	C + HA	S + HA		●	●	●			●	●		●	●				●	●	●	●		11
S8	1	a	Emadedin	2018	x BM-MSCs	C	Saline		●	●			●	●	●		●			●	●	●	●		●		11
S22	1	a	Kim	2018	y Ch-TGFß	C	Saline																●	●			2
S26	1	a	Kuah	2018	y ADSCs	C	Saline			●	●	●		●	●		●					●	●		●		10
S21	1	a	Khalifeh Soltani	2019	y P-MSCs	C	Saline			●												●			●		3
S28	1	a	Lee	2019	x ADSCs	C	Saline			●	●	●		●			●		●	●	●		●	●	●		11
S11	1	a	Garza	2020	x ADRCs	C	RS									●	●		●						●		4
S51	2	a	Vega	2015	y BM-MSCs	C	HA	●	●	●	●	●		●	●		●	●		●	●	●	●	●	●		15
S52	2	a	Wang	2016	y hUC-MSCs	C	HA	●			●												●				3
S12	2	a	Goncars	2017	x BMACBMAC	C	HA														●						1
S29	2	a	Lu	2019	x ADSCs	C	HA	●		●					●		●	●		●	●		●	●	●	●	11
S31	2	a	Matas	2019	y hUC-MSCs	C	HA	●		●	●		●	●	●								●		●		8
S3	2	a	Anz	2020	x BMACBMAC	C	PRP									●											1
S10	3	a	Garay-Mendoza	2018	x BMACBMAC	C	OA									●	●				●						3
S44	3	a	Song	2018	x ADSCs	C	C				●								●								2
S9	3	a	Freitag	2019	x ADSCs	C	CM			●							●	●	●		●		●		●		7
S4	3	a	Bastos	2020	x BM-MSCs	C	C + PRP +CS						●				●				●						2
S20	3	c	Jo	2014	x ADSCs	C	C												●								1
S36	3	c	Pers	2016	x ADSCs	C	C				●								●								2
S19	3	c	Jo	2017	x ADSCs	C	C				●								●								2
S35	3	c	Pers	2018	x ADSCs	C	C														●						1
S32	3	d	Mautner	2019	x MFF	C	BMACBMAC									●											1

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Table S6 (cont.)

R	Ca	T	First author	Year	Cells	T	Control	Reference no. in the main text																							N
								15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33					
S54	3	d	Yokota	2019	x ADRCs	C	C									●			●												2
S50	4	a	Varma	2010	x BM-MSCs	C + AD	AD		●																							1
S53	4	a	Wong	2013	x BM-MSCs	C + MF + HTO + HA	MF + HTO + HA					●					●	●														3
S25	4	a	Koh	2014	x ADRCs	C + AD + HTO + PRP	AD + HTO + PRP										●							●							2
S27	4	a	Lamo-Espinosa	2016	x BM-MSCs	C + HA	HA	●	●	●		●		●	●		●	●		●		●	●		●						12
S5	4	a	Bastos	2018	x BM-MSCs	C + PRP	C				●												●								3
S56	4	a	Zhang	2018	x ADSCs	C + HA	C													●											1
S41	4	b	Shapiro	2017	x BMACBMAC	C + PPP	Saline					●																			1
S16	4	b	Hong	2019	x ADRCs	C + AD	HA + AD										●		●							●	●				4
S40	4	b	Shapiro	2019	x BMACBMAC	C + PPP	Saline																			●					1
S23	4	c	Koh	2012	x ADSCs	C + AD + PRP	AD + PRP				●						●	●						●							4
S33	4	c	Nguyen	2017	x ADRCs	C + AD + MF + PRP	AD + MF												●												1
S47	4	c	Tran	2019	x ADRCs	C + AD + MF	AD + MF										●		●												2
S24	5	e	Koh	2013	x ADRCs	C + PRP + HA	None												●												1
S34	5	e	Orozco	2013	x BM-MSCs	C	None														●										1
S43	5	e	Soler	2016	x BM-MSCs	C	None														●										1
S2	5	e	Al-Najar	2017	x BM-MSCs	C	None														●										1
S18	5	e	Hudetz	2017	x MFF	C	None														●										1
S55	5	e	Yokota	2017	x ADRCs	C	None									●					●										2
S42	5	e	Shaw	2018	x BMACBMAC	C	None														●										1
S45	5	e	Spasovski	2018	x ADSCs	C	None				●								●												2
S46	5	e	Themistocleous	2018	x BMACBMAC	C	None									●															1
S17	5	e	Hudetz	2019	x MFF	C	None									●			●		●										3
S37	5	e	Roato	2019	x CLL	C + AD	None												●												1
S39	5	e	Schiavone Panni	2019	x MFF	C + AD	None												●												1
S48	5	e	Tsubosaka	2020	x ADRCs	C	None									●					●										2
S38	6	a	Saw	2013	x pBSCs	C + MF + HA	HA					●																			1
S1	6	a	Akgun	2015	x S-MSCs	C in Sc + AD	MACI																	●							1
S15	6	a	Hashimoto	2019	x BM-MSCs	C + MF	MF																	●							1
S49	6	a	Vangsness	2014	y BM-MSCs				●								●	●													3
S6	1	a	Bhattacharia	2010	---							●																			1
S30			Lv	2015	U												●														1
S14			Ha	2018	U				●																						1

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Table S7 | Details of the sub-analyses performed in a meta-analysis by Jiang et al.[28].

Abbreviations: allo = allogeneic cells; auto = autologous cells; C = category of study as outlined in Table S2; O = origin of cells; QC = quality criteria (outlined in Table 1 in the main text; a point indicates that the corresponding quality criterion was fulfilled); R = reference number; T = type of study as outlined in Table S3; Y = year of publication. The abbreviations of the cell types and treatments are provided in Table S6.

WOMAC Total score reported at 6 months post treatment

R	C	T	First author	Y	Cells	Treatment	Control	O
S31	2	a	Matas	2019	hUC-MSCs	C	HA	allo
S51	2	a	Vega	2015	BM-MSCs	C	HA	allo
S29	2	a	Lu	2019	ADSCs	C	HA	auto
S52	2	a	Wang	2016	hUC-MSCs	C	HA	allo

QC	1	2	3	4	5	6	7	8
	●	●	●	●			●	●

WOMAC Total score reported at 12 months post treatment

R	C	T	First author	Y	Cells	Treatment	Control	O
S31	2	a	Matas	2019	hUC-MSCs	C	HA	allo
S51	2	a	Vega	2015	BM-MSCs	C	HA	allo
S29	2	a	Lu	2019	ADSCs	C	HA	auto

QC	1	2	3	4	5	6	7	8
	●	●	●	●			●	●

WOMAC Pain score reported at 6 months post treatment

R	C	T	First author	Y	Cells	Treatment	Control	O
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S29	2	a	Lu	2019	ADSCs	C	HA	auto
S31	2	a	Matas	2019	hUC-MSCs	C	HA	allo
S51	2	a	Vega	2015	BM-MSCs	C	HA	allo

QC	1	2	3	4	5	6	7	8
	●	●	●	●			●	●

WOMAC Stiffness score reported at 6 months post treatment

R	C	T	First author	Y	Cells	Treatment	Control	O
S29	2	a	Lu	2019	ADSCs	C	HA	auto
S31	2	a	Matas	2019	hUC-MSCs	C	HA	allo

QC	1	2	3	4	5	6	7	8
	●	●	●	●			●	●

WOMAC Stiffness score reported at 12 months post treatment

R	C	T	First author	Y	Cells	Treatment	Control	O
S29	2	a	Lu	2019	ADSCs	C	HA	auto
S31	2	a	Matas	2019	hUC-MSCs	C	HA	allo

QC	1	2	3	4	5	6	7	8
	●	●	●	●			●	●

WOMAC Function score reported at 6 months post treatment

R	C	T	First author	Y	Cells	Treatment	Control	O
S29	2	a	Lu	2019	ADSCs	C	HA	auto
S31	2	a	Matas	2019	hUC-MSCs	C	HA	allo

QC	1	2	3	4	5	6	7	8
	●	●	●	●			●	●

WOMAC Function score reported at 12 months post treatment

R	C	T	First author	Y	Cells	Treatment	Control	O
S29	2	a	Lu	2019	ADSCs	C	HA	auto
S31	2	a	Matas	2019	hUC-MSCs	C	HA	allo

QC	1	2	3	4	5	6	7	8
	●	●	●	●			●	●

VAS Pain score reported at 6 months post treatment

R	C	T	First author	Y	Cells	Treatment	Control	O
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S29	2	a	Lu	2019	ADSCs	C	HA	auto
S31	2	a	Matas	2019	hUC-MSCs	C	HA	allo
S51	2	a	Vega	2015	BM-MSCs	C	HA	allo

QC	1	2	3	4	5	6	7	8
	●	●	●	●			●	●

VAS pain score reported at 12 months post treatment

R	C	T	First author	Y	Cells	Treatment	Control	O
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S29	2	a	Lu	2019	ADSCs	C	HA	auto
S31	2	a	Matas	2019	hUC-MSCs	C	HA	allo
S51	2	a	Vega	2015	BM-MSCs	C	HA	allo

QC	1	2	3	4	5	6	7	8
	●	●	●	●			●	●

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Whole-Organ Magnetic Resonance Imaging (WORMS) score reported at 6 months post treatment

R	C	T	First author	Y	Cells	Treatment	Control	O
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S31	2	a	Matas	2019	hUC-MSCs	C	HA	allo

QC	1	2	3	4	5	6	7	8
	●	●	●	●			●	●

WORMS score reported at 12 months post treatment

R	C	T	First author	Y	Cells	Treatment	Control	O
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S31	2	a	Matas	2019	hUC-MSCs	C	HA	allo

QC	1	2	3	4	5	6	7	8
	●	●	●	●			●	●

LEQUESNE score reported at 6 months post treatment

R	C	T	First author	Y	Cells	Treatment	Control	O
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S51	2	a	Vega	2015	BM-MSCs	C	HA	allo

QC	1	2	3	4	5	6	7	8
	●	●	●	●			●	●

LEQUESNE score reported at 12 months post treatment

R	C	T	First author	Y	Cells	Treatment	Control	O
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S51	2	a	Vega	2015	BM-MSCs	C	HA	allo

QC	1	2	3	4	5	6	7	8
	●	●	●	●			●	●

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Table S8 | Details of the sub-analyses performed in a meta-analysis by Qu and Sun[30].

Abbreviations: allo = allogeneic cells; auto = autologous cells; C = category of study as outlined in Table S2; O = origin of cells; QC = quality criteria (outlined in Table 1 in the main text; a point indicates that the corresponding quality criterion was fulfilled); R = reference number; T = type of study as outlined in Table S3; Y = year of publication. The abbreviations of the cell types and treatments are provided in Table S6.

VAS Pain score reported at 3 months post treatment

R	C	T	First author	Y	Cells	Treatment	Control	O
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S50	4	a	Varma	2010	BM-MSCs	C + AD	AD	?
S14			Ha	2018				

QC	1	2	3	4	5	6	7	8
	●	●	●	●	●	●	●	

VAS Pain score reported at 6 months post treatment

R	C	T	First author	Y	Cells	Treatment	Control	O
S8	1	a	Emadedin	2018	BM-MSCs	C	S	auto
S13	1	a	Gupta	2016	BM-MSCs	C	S	allo
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S50	4	a	Varma	2010	BM-MSCs	C + AD	AD	?
S49	6	a	Vangsness	2014	BM-MSCs	C	S	allo
S49	6	a	Vangsness	2014	BM-MSCs	C	S	allo
S14			Ha	2018				

QC	1	2	3	4	5	6	7	8
	●		●	●	●		●	

VAS Pain score reported at 12 months post treatment

R	C	T	First author	Y	Cells	Treatment	Control	O
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S50	4	a	Varma	2010	BM-MSCs	C + AD	AD	?
S51	2	a	Vega	2015	BM-MSCs	C	HA	allo
S49	6	a	Vangsness	2014	BM-MSCs	C	S	allo
S49	6	a	Vangsness	2014	BM-MSCs	C	S	allo
S14			Ha	2018				

QC	1	2	3	4	5	6	7	8
	●		●	●		●	●	

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VAS Pain score reported at 24 months post treatment

R	C	T	First author	Y	Cells	Treatment	Control	O
S49	6	a	Vangsness	2014	BM-MSCs	C	S	allo
S49	6	a	Vangsness	2014	BM-MSCs	C	S	allo

QC	1	2	3	4	5	6	7	8
	●		●	●	●	●	●	

WOMAC Pain score reported at 3 months post treatment

R	C	T	First author	Y	Cells	Treatment	Control	O
S13	4	a	Gupta	2016	BM-MSCs	C	S + HA	allo
S13	4	a	Gupta	2016	BM-MSCs	C	S + HA	allo
S13	4	a	Gupta	2016	BM-MSCs	C	S + HA	allo
S13	4	a	Gupta	2016	BM-MSCs	C	S + HA	allo

QC	1	2	3	4	5	6	7	8
	●	●	●	●	●	●	●	

WOMAC Pain score reported at 6 months post treatment

R	C	T	First author	Y	Cells	Treatment	Control	O
S8	1	a	Emadedin	2018	BM-MSCs	C	S	auto
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo

QC	1	2	3	4	5	6	7	8
	●	●	●	●	●		●	

WOMAC Pain score reported at 12 months post treatment

R	C	T	First author	Y	Cells	Treatment	Control	O
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S51	2	a	Vega	2015	BM-MSCs	C + HA	HA	allo

QC	1	2	3	4	5	6	7	8
	●	●	●	●			●	

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Table S9 | Details of the sub-analyses performed in a meta-analysis by Ma et al.[18].

Abbreviations: allo = allogeneic cells; auto = autologous cells; C = category of study as outlined in Table S2; O = origin of cells; QC = quality criteria (outlined in Table 1 in the main text; a point indicates that the corresponding quality criterion was fulfilled); R = reference number; T = type of study as outlined in Table S3; Y = year of publication. The abbreviations of the cell types and treatments are provided in Table S6.

VAS Pain score

R	C	T	First author	Y	Cells	Treatment	Control	O
S8	1	a	Emadedin	2018	BM-MSCs	C	S	auto
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S29	2	a	Lu	2019	ADSCs	C	HA	auto
S31	2	a	Matas	2019	hUC-MSCs	C	HA	allo
S51	2	a	Vega	2015	BM-MSCs	C	HA	allo

QC	1	2	3	4	5	6	7	8
	●	●	●	●			●	●

WOMAC Total score

R	C	T	First author	Y	Cells	Treatment	Control	O
S8	1	a	Emadedin	2018	BM-MSCs	C	S	auto
S9	3	a	Freitag	2019	ADSCs	C	CM	auto
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S29	2	a	Lu	2019	ADSCs	C	HA	auto
S31	2	a	Matas	2019	hUC-MSCs	C	HA	allo
S51	2	a	Vega	2015	BM-MSCs	C	HA	allo

QC	1	2	3	4	5	6	7	8
	●	●	●	●			●	●

WOMAC Pain score

R	C	T	First author	Y	Cells	Treatment	Control	O
S8	1	a	Emadedin	2018	BM-MSCs	C	S	auto
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S29	2	a	Lu	2019	ADSCs	C	HA	auto
S31	2	a	Matas	2019	hUC-MSCs	C	HA	allo
S51	2	a	Vega	2015	BM-MSCs	C	HA	allo

QC	1	2	3	4	5	6	7	8
	●	●	●	●			●	●

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WOMAC Stiffness score

R	C	T	First author	Y	Cells	Treatment	Control	O
S8	1	a	Emadedin	2018	BM-MSCs	C	S	auto
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S29	2	a	Lu	2019	ADSCs	C	HA	auto
S31	2	a	Matas	2019	hUC-MSCs	C	HA	allo

QC	1	2	3	4	5	6	7	8
	●	●	●	●			●	●

WOMAC Function score

R	C	T	First author	Y	Cells	Treatment	Control	O
S8	1	a	Emadedin	2018	BM-MSCs	C	S	auto
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S29	2	a	Lu	2019	ADSCs	C	HA	auto
S31	2	a	Matas	2019	hUC-MSCs	C	HA	allo

QC	1	2	3	4	5	6	7	8
	●	●	●	●			●	●

Whole-Organ Magnetic Resonance Imaging (WORMS) score

R	C	T	First author	Y	Cells	Treatment	Control	O
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S31	2	a	Matas	2019	hUC-MSCs	C	HA	allo

QC	1	2	3	4	5	6	7	8
	●	●	●	●			●	●

Cartilage volume

R	C	T	First author	Y	Cells	Treatment	Control	O
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S28	1	a	Lee	2019	ADSCs	C	S	auto
S29	2	a	Lu	2019	ADSCs	C	HA	auto

QC	1	2	3	4	5	6	7	8
	●	●	●	●			●	●

Number of patients with adverse events

R	C	T	First author	Y	Cells	Treatment	Control	O
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S21	1	a	Khalifeh Soltani	2019	P-MSCs	C	S	allo
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S28	1	a	Lee	2019	ADSCs	C	S	auto
S29	2	a	Lu	2019	ADSCs	C	HA	auto

QC	1	2	3	4	5	6	7	8
	●	●	●	●			●	●

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Table S10 | Details of the sub-analyses performed in a meta-analysis by Huang et al.[16].

Abbreviations: allo = allogeneic cells; auto = autologous cells; C = category of study as outlined in Table S2; O = origin of cells; QC = quality criteria (outlined in Table 1 in the main text; a point indicates that the corresponding quality criterion was fulfilled); R = reference number; T = type of study as outlined in Table S3; Y = year of publication. The abbreviations of the cell types and treatments are provided in Table S6.

VAS Pain score reported at 3 months post treatment

R	C	T	First author	Y	Cells	Treatment	Control	O
S6			Bhattacharia	2010				
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S41	4	b	Shapiro	2017	BMACBMAC	C + PPP	S	auto

QC	1	2	3	4	5	6	7	8
	●	●						

VAS Pain score reported at 6 months post treatment

R	C	T	First author	Y	Cells	Treatment	Control	O
S6			Bhattacharia	2010				
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S41	4	b	Shapiro	2017	BMACBMAC	C + PPP	S	auto

QC	1	2	3	4	5	6	7	8
	●	●						

VAS pain score reported at 12 months post treatment

R	C	T	First author	Y	Cells	Treatment	Control	O
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S41	4	b	Shapiro	2017	BMACBMAC	C + PPP	S	auto
S51	2	a	Vega	2015	BM-MSCs	C	HA	allo

QC	1	2	3	4	5	6	7	8
	●	●	●					

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WOMAC Pain score reported at 3 months post treatment

R	C	T	First author	Y	Cells	Treatment	Control	O
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto

QC	1	2	3	4	5	6	7	8
	●	●	●	●	●		●	

WOMAC Pain score reported at 6 months post treatment

R	C	T	First author	Y	Cells	Treatment	Control	O
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto

QC	1	2	3	4	5	6	7	8
	●	●	●	●	●		●	

WOMAC Pain score reported at 12 months post treatment

R	C	T	First author	Y	Cells	Treatment	Control	O
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S51	2	a	Vega	2015	BM-MSCs	C	HA	allo

QC	1	2	3	4	5	6	7	8
	●	●	●	●	●		●	

WOMAC Stiffness score reported at 3 months post treatment

R	C	T	First author	Y	Cells	Treatment	Control	O
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto

QC	1	2	3	4	5	6	7	8
	●	●	●	●	●		●	

WOMAC Stiffnes score reported at 6 months post treatment

R	C	T	First author	Y	Cells	Treatment	Control	O
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto

QC	1	2	3	4	5	6	7	8
	●	●	●	●	●		●	

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WOMAC Stiffness score reported at 12 months post treatment

R	C	T	First author	Y	Cells	Treatment	Control	O
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto

QC	1	2	3	4	5	6	7	8
	●	●	●	●	●		●	

WOMAC Function score reported at 3 months post treatment

R	C	T	First author	Y	Cells	Treatment	Control	O
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto

QC	1	2	3	4	5	6	7	8
	●	●	●	●	●		●	

WOMAC Function score reported at 6 months post treatment

R	C	T	First author	Y	Cells	Treatment	Control	O
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto

QC	1	2	3	4	5	6	7	8
	●	●	●	●	●		●	

WOMAC Function score reported at 12 months post treatment

R	C	T	First author	Y	Cells	Treatment	Control	O
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto

QC	1	2	3	4	5	6	7	8
	●	●	●	●	●		●	

International Knee Documentation Committee (IKDC) score reported at 6 months post treatment

R	C	T	First author	Y	Cells	Treatment	Control	O
S38	6	a	Saw	2013	pBSCs	C + MF + HA	MF + HA	auto
S53	4	a	Wong	2013	BM-MSCs	C + MF + HTO + HA	MF + HTO + HA	auto

QC	1	2	3	4	5	6	7	8
	●		●	●	●	●	●	●

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International Knee Documentation Committee (IKDC) score reported at 12 months post treatment

R	C	T	First author	Y	Cells	Treatment	Control	O
S38	6	a	Saw	2013	pBSCs	C + MF + HA	MF + HA	auto
S53	4	a	Wong	2013	BM-MSCs	C + MF + HTO + HA	MF + HTO + HA	auto

QC	1	2	3	4	5	6	7	8
	●		●	●	●	●	●	●

International Knee Documentation Committee (IKDC) score reported at 24 months post treatment

R	C	T	First author	Y	Cells	Treatment	Control	O
S38	6	a	Saw	2013	pBSCs	C + MF + HA	MF + HA	auto
S53	4	a	Wong	2013	BM-MSCs	C + MF + HTO + HA	MF + HTO + HA	auto

QC	1	2	3	4	5	6	7	8
	●		●	●	●	●	●	●

Adverse events

R	C	T	First author	Y	Cells	Treatment	Control	O
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S28	1	a	Lee	2019	ADSCs	C	S	auto

QC	1	2	3	4	5	6	7	8
	●	●	●	●	●		●	●

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Table S11 | Details of the sub-analyses performed in a meta-analysis by Wei et al.[32].

Abbreviations: allo = allogeneic cells; auto = autologous cells; C = category of study as outlined in Table S2; O = origin of cells; QC = quality criteria (outlined in Table 1 in the main text; a point indicates that the corresponding quality criterion was fulfilled); R = reference number; T = type of study as outlined in Table S3; Y = year of publication. The abbreviations of the cell types and treatments are provided in Table S6.

VAS Pain score

R	C	T	First author	Y	Cells	Treatment	Control	O
S51	2	a	Vega	2015	BM-MSCs	C	HA	allo
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S8	1	a	Emadedin	2018	BM-MSCs	C	S	auto
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S31	2	a	Matas	2019	hUC-MSCs	C	HA	allo
S28	1	a	Lee	2019	ADSCs	C	S	auto

QC	1	2	3	4	5	6	7	8
	●	●	●	●			●	●

Functional improvement

R	C	T	First author	Y	Cells	Treatment	Control	O
S51	2	a	Vega	2015	BM-MSCs	C	HA	allo
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S8	1	a	Emadedin	2018	BM-MSCs	C	S	auto
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S31	2	a	Matas	2019	hUC-MSCs	C	HA	allo
S28	1	a	Lee	2019	ADSCs	C	S	auto

QC	1	2	3	4	5	6	7	8
	●	●	●	●			●	●

Structural assessment

R	C	T	First author	Y	Cells	Treatment	Control	O
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S31	2	a	Matas	2019	hUC-MSCs	C	HA	allo
S28	1	a	Lee	2019	ADSCs	C	S	auto

QC	1	2	3	4	5	6	7	8
	●	●	●	●			●	●

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Table S12 | Details of the sub-analyses performed in a meta-analysis by Wang et al.[20].

Abbreviations: allo = allogeneic cells; auto = autologous cells; C = category of study as outlined in Table S2; O = origin of cells; QC = quality criteria (outlined in Table 1 in the main text; a point indicates that the corresponding quality criterion was fulfilled); R = reference number; T = type of study as outlined in Table S3; Y = year of publication. The abbreviations of the cell types and treatments are provided in Table S6.

Adverse events

R	C	T	First author	Y	Cells	Treatment	Control	O
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S29	2	a	Lu	2019	ADSCs	C	HA	auto
S31	2	a	Matas	2019	hUC-MSCs	C	HA	allo
S51	2	a	Vega	2015	BM-MSCs	C	HA	allo

QC	1	2	3	4	5	6	7	8
	●	●	●	●			●	●

VAS score low dose

R	C	T	First author	Y	Cells	Treatment	Control	O
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S31	2	a	Matas	2019	hUC-MSCs	C	HA	allo

QC	1	2	3	4	5	6	7	8
	●	●	●	●			●	●

VAS score medium dose

R	C	T	First author	Y	Cells	Treatment	Control	O
S8	1	a	Emadedin	2018	BM-MSCs	C	S	auto
S51	2	a	Vega	2015	BM-MSCs	C	HA	allo

QC	1	2	3	4	5	6	7	8
	●	●	●	●			●	●

VAS scire high dose

R	C	T	First author	Y	Cells	Treatment	Control	O
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S29	2	a	Lu	2019	ADSCs	C	HA	auto

QC	1	2	3	4	5	6	7	8
	●	●	●	●			●	●

WOMAC Pain score low dose

R	C	T	First author	Y	Cells	Treatment	Control	O
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S31	2	a	Matas	2019	hUC-MSCs	C	HA	allo

QC	1	2	3	4	5	6	7	8
	●	●	●	●			●	●

WOMAC Pain score medium dose

R	C	T	First author	Y	Cells	Treatment	Control	O
S8	1	a	Emadedin	2018	BM-MSCs	C	S	auto
S51	2	a	Vega	2015	BM-MSCs	C	HA	allo

QC	1	2	3	4	5	6	7	8
	●	●	●	●			●	●

WOMAC Pain score high dose

R	C	T	First author	Y	Cells	Treatment	Control	O
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S29	2	a	Lu	2019	ADSCs	C	HA	auto

QC	1	2	3	4	5	6	7	8
	●	●	●	●			●	●

WOMAC Stiffness score low dose

R	C	T	First author	Y	Cells	Treatment	Control	O
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S31	2	a	Matas	2019	hUC-MSCs	C	HA	allo

QC	1	2	3	4	5	6	7	8
	●	●	●	●			●	●

WOMAC Stiffness score medium dose

R	C	T	First author	Y	Cells	Treatment	Control	O
S8	1	a	Emadedin	2018	BM-MSCs	C	S	auto

QC	1	2	3	4	5	6	7	8
		●	●	●	●	●	●	●

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WOMAC Stiffness score high dose

R	C	T	First author	Y	Cells	Treatment	Control	O
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S29	2	a	Lu	2019	ADSCs	C	HA	auto

QC	1	2	3	4	5	6	7	8
	●	●	●	●			●	●

WOMAC Physical Function score low dose

R	C	T	First author	Y	Cells	Treatment	Control	O
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S31	2	a	Matas	2019	hUC-MSCs	C	HA	allo

QC	1	2	3	4	5	6	7	8
	●	●	●	●			●	●

WOMAC Physical Function score medium low dose

R	C	T	First author	Y	Cells	Treatment	Control	O
S8	1	a	Emadedin	2018	BM-MSCs	C	S	auto

QC	1	2	3	4	5	6	7	8
		●	●	●	●	●	●	●

WOMAC Physical Function score high dose

R	C	T	First author	Y	Cells	Treatment	Control	O
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S29	2	a	Lu	2019	ADSCs	C	HA	auto

QC	1	2	3	4	5	6	7	8
	●	●	●	●			●	●

WOMAC Total score low dose

R	C	T	First author	Y	Cells	Treatment	Control	O
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S31	2	a	Matas	2019	hUC-MSCs	C	HA	allo

QC	1	2	3	4	5	6	7	8
	●	●	●	●			●	●

WOMAC Total score medium dose

R	C	T	First author	Y	Cells	Treatment	Control	O
S8	1	a	Emadedin	2018	BM-MSCs	C	S	auto
S51	2	a	Vega	2015	BM-MSCs	C	HA	allo

QC	1	2	3	4	5	6	7	8
	●	●	●	●			●	●

WOMAC Total score high dose

R	C	T	First author	Y	Cells	Treatment	Control	O
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S29	2	a	Lu	2019	ADSCs	C	HA	auto

QC	1	2	3	4	5	6	7	8
	●	●	●	●			●	●

Whole-Organ Magnetic Resonance Imaging (WORMS) score reported at 6 months post treatment

R	C	T	First author	Y	Cells	Treatment	Control	O
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S+ HA	allo
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S31	2	a	Matas	2019	hUC-MSCs	C	HA	allo

QC	1	2	3	4	5	6	7	8
	●	●	●	●			●	●

WORMS score reported at 12 months post treatment

R	C	T	First author	Y	Cells	Treatment	Control	O
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S31	2	a	Matas	2019	hUC-MSCs	C	HA	allo

QC	1	2	3	4	5	6	7	8
	●	●	●	●			●	●

VAS Pain score bmsc

R	C	T	First author	Y	Cells	Treatment	Control	O
S8	1	a	Emadedin	2018	BM-MSCs	C	S	auto
S13	1	a	Gupta	2016	BM-MSCs	C	S	allo
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S51	2	a	Vega	2015	BM-MSCs	C	HA	allo

QC	1	2	3	4	5	6	7	8
	●	●	●	●			●	●

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VAS Pain score admsc and ucmsc

R	C	T	First author	Y	Cells	Treatment	Control	O
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S29	2	a	Lu	2019	ADSCs	C	HA	auto
S31	2	a	Matas	2019	hUC-MSCs	C	HA	allo

QC	1	2	3	4	5	6	7	8
	●	●	●	●			●	●

WOMAC Pain score bmsc

R	C	T	First author	Y	Cells	Treatment	Control	O
S8	1	a	Emadedin	2018	BM-MSCs	C	S	auto
S13	1	a	Gupta	2016	BM-MSCs	C	S	allo
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S51	2	a	Vega	2015	BM-MSCs	C	HA	allo

QC	1	2	3	4	5	6	7	8
	●	●	●	●			●	●

WOMAC Pain score admsc and ucmsc

R	C	T	First author	Y	Cells	Treatment	Control	O
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S29	2	a	Lu	2019	ADSCs	C	HA	auto
S31	2	a	Matas	2019	hUC-MSCs	C	HA	allo

QC	1	2	3	4	5	6	7	8
	●	●	●	●			●	●

VAS Pain score allogenic

R	C	T	First author	Y	Cells	Treatment	Control	O
S13	1	a	Gupta	2016	BM-MSCs	C	S	allo
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S31	2	a	Matas	2019	hUC-MSCs	C	HA	allo
S51	2	a	Vega	2015	BM-MSCs	C	HA	allo

QC	1	2	3	4	5	6	7	8
	●	●	●	●		●	●	●

VAS Pain score autologous

R	C	T	First author	Y	Cells	Treatment	Control	O
S8	1	a	Emadedin	2018	BM-MSCs	C	S	auto
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S29	2	a	Lu	2019	ADSCs	C	HA	auto

QC	1	2	3	4	5	6	7	8
	●	●	●	●		●	●	●

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WOMAC pain score allogenic

R	C	T	First author	Y	Cells	Treatment	Control	O
S13	1	a	Gupta	2016	BM-MSCs	C	S	allo
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S31	2	a	Matas	2019	hUC-MSCs	C	HA	allo
S51	2	a	Vega	2015	BM-MSCs	C	HA	allo

QC	1	2	3	4	5	6	7	8
	●	●	●	●		●	●	●

WOMAC score autologous

R	C	T	First author	Y	Cells	Treatment	Control	O
S8	1	a	Emadedin	2018	BM-MSCs	C	S	auto
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S29	2	a	Lu	2019	ADSCs	C	HA	auto

QC	1	2	3	4	5	6	7	8
	●	●	●	●		●	●	●

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Table S13 | Details of the sub-analyses performed in a meta-analysis by Jeyaraman et al.[27].

Abbreviations: allo = allogeneic cells; auto = autologous cells; C = category of study as outlined in Table S2; O = origin of cells; QC = quality criteria (outlined in Table 1 in the main text; a point indicates that the corresponding quality criterion was fulfilled); R = reference number; T = type of study as outlined in Table S3; Y = year of publication. The abbreviations of the cell types and treatments are provided in Table S6.

VAS Pain score reported at 6 months post treatment using bone marrow-derived cells

R	C	T	First author	Y	Cells	Treatment	Control	O
S49	6	a	Vangsness	2014	BM-MSCs	C	S	allo
S49	6	a	Vangsness	2014	BM-MSCs	C	S	allo
S10	3	a	Garay-Mendoza	2018	BMACBMAC	C	OA	auto
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S8	1	a	Emadedin	2018	BM-MSCs	C	S	auto
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo

QC	1	2	3	4	5	6	7	8
	●		●	●	●			

VAS Pain score reported at 12 months post treatment using bone marrow-derived cells

R	C	T	First author	Y	Cells	Treatment	Control	O
S49	6	a	Vangsness	2014	BM-MSCs	C	S	allo
S49	6	a	Vangsness	2014	BM-MSCs	C	S	allo
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo

QC	1	2	3	4	5	6	7	8
	●		●	●	●		●	

VAS Pain score reported at 24 months post treatment using bone marrow-derived cells

R	C	T	First author	Y	Cells	Treatment	Control	O
S49	6	a	Vangsness	2014	BM-MSCs	C	S	allo
S49	6	a	Vangsness	2014	BM-MSCs	C	S	allo

QC	1	2	3	4	5	6	7	8
	●		●	●	●	●	●	

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VAS Pain score reported at 6 months post treatment using adipose-derived cells

R	C	T	First author	Y	Cells	Treatment	Control	O
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S29	2	a	Lu	2019	ADSCs	C	HA	auto
S28	1	a	Lee	2019	ADSCs	C	S	auto
S16	4	b	Hong	2019	ADRCs	C + AD	HA + AD	auto

QC	1	2	3	4	5	6	7	8
	●	●	●				●	

VAS Pain score reported at 12 months post treatment using adipose-derived cells

R	C	T	First author	Y	Cells	Treatment	Control	O
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S29	2	a	Lu	2019	ADSCs	C	HA	auto
S28	1	a	Lee	2019	ADSCs	C	S	auto
S9	3	a	Freitag	2019	ADSCs	C	CM	auto
S9	3	a	Freitag	2019	ADSCs	C	CM	auto

QC	1	2	3	4	5	6	7	8
	●	●	●	●			●	

VAS Pain score reported at 24 months post treatment using adipose-derived cells

R	C	T	First author	Y	Cells	Treatment	Control	O
S23	4	c	Koh	2012	ADRCs	C + AD + PRP	AD + PRP	auto
S25	4	a	Koh	2014	ADRCs	C + AD + HTO + PRP	AD + HTO + PRP	auto
S47	4	c	Tran	2019	ADRCs	C + AD + MF	AD + MF	auto

QC	1	2	3	4	5	6	7	8
	●	●	●		●	●	●	●

WOMAC Total score reported at 6 months post treatment using bone marrow-derived cells

R	C	T	First author	Y	Cells	Treatment	Control	O
S10	3	a	Garay-Mendoza	2018	BMACBMAC	C	OA	auto
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S30			Lv	2015	BM-MSCs	?	?	auto
S8	1	a	Emadedin	2018	BM-MSCs	C	S	auto

QC	1	2	3	4	5	6	7	8
	●	●	●	●	●	●		

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WOMAC Total score reported at 12 months post treatment using bone marrow-derived cells

R	C	T	First author	Y	Cells	Treatment	Control	O
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S30			Lv	2015	BM-MSCs	?	?	auto
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S51	2	a	Vega	2015	BM-MSCs	C + HA	HA	allo

QC	1	2	3	4	5	6	7	8
	●	●	●	●			●	

WOMAC Total score reported at 6 months post treatment using adipose-derived cells

R	C	T	First author	Y	Cells	Treatment	Control	O
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S11	1	a	Garza	2020	ADRCs	C	RS	auto
S11	1	a	Garza	2020	ADRCs	C	RS	auto
S29	2	a	Lu	2019	ADSCs	C	HA	auto
S28	1	a	Lee	2019	ADSCs	C	S	auto

QC	1	2	3	4	5	6	7	8
	●	●	●	●				

WOMAC Total score reported at 12 months post treatment using adipose-derived cells

R	C	T	First author	Y	Cells	Treatment	Control	O
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S11	1	a	Garza	2020	ADRCs	C	RS	auto
S11	1	a	Garza	2020	ADRCs	C	RS	auto
S29	2	a	Lu	2019	ADSCs	C	HA	auto
S9	3	a	Freitag	2019	ADSCs	C	CM	auto
S9	3	a	Freitag	2019	ADSCs	C	CM	auto
S47	4	c	Tran	2019	ADRCs	C + AD + MF	AD + MF	auto

QC	1	2	3	4	5	6	7	8
	●	●	●					

Lysholm score reported at 12 months post treatment using bone marrow-derived cells

R	C	T	First author	Y	Cells	Treatment	Control	O
S49	6	a	Vangsness	2014	BM-MSCs	C	S	allo
S49	6	a	Vangsness	2014	BM-MSCs	C	S	allo
S53	4	a	Wong	2013	BM-MSCs	C + MF + HTO + HA	MF + HTO + HA	auto

QC	1	2	3	4	5	6	7	8
	●		●	●	●		●	

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Lysholm score reported at 24 months post treatment using bone marrow-derived cells

R	C	T	First author	Y	Cells	Treatment	Control	O
S49	6	a	Vangsness	2014	BM-MSCs	C	S	allo
S49	6	a	Vangsness	2014		C	S	allo
S53	4	a	Wong	2013	BM-MSCs	C + MF + HTO + HA	MF + HTO + HA	auto

QC	1	2	3	4	5	6	7	8
	●		●	●	●		●	

Lysholm score reported at 24 months post treatment using adipose-derived cells

R	C	T	First author	Y	Cells	Treatment	Control	O
S47	4	c	Tran	2019	ADRCs	C + AD + MF	AD + MF	auto
S23	4	c	Koh	2012	ADRCs	C + AD + PRP	AD + PRP	auto
S25	4	a	Koh	2014	ADRCs	C + AD + HTO + PRP	AD + HTO + PRP	auto

QC	1	2	3	4	5	6	7	8
	●	●	●		●	●	●	●

KOOS score reported at 12 months post treatment using bone marrow-derived cells

R	C	T	First author	Y	Cells	Treatment	Control	O
S4	3	a	Bastos	2020	BM-MSCs	C	C + PRP	auto
S4	3	a	Bastos	2020	BM-MSCs	C	C + PRP	auto

QC	1	2	3	4	5	6	7	8
	●	●	●	●	●	●	●	

KOOS score reported at 12 months post treatment using adipose-derived cells

R	C	T	First author	Y	Cells	Treatment	Control	O
S9	3	a	Freitag	2019	ADSCs	C	CM	auto
S9	3	a	Freitag	2019	ADSCs	C	CM	auto
S28	1	a	Lee	2019	ADSCs	C	S	auto

QC	1	2	3	4	5	6	7	8
	●	●	●	●	●	●	●	

Whole-Organ Magnetic Resonance Imaging (WORMS) score reported at 12 months post treatment using bone marrow-derived cells

R	C	T	First author	Y	Cells	Treatment	Control	O
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S53	4	a	Wong	2013	BM-MSCs	C + MF + HTO + HA	MF + HTO + HA	auto
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo

QC	1	2	3	4	5	6	7	8
	●	●	●	●	●		●	

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WORMS score reported at 12 months post treatment using adipose-derived cells

R	C	T	First author	Y	Cells	Treatment	Control	O
S29	2	a	Lu	2019	ADSCs	C	HA	auto
S28	1	a	Lee	2019	ADSCs	C	S	auto
S16	4	b	Hong	2019	ADRCs	C + AD	HA + AD	auto

QC	1	2	3	4	5	6	7	8
	●	●	●	0	0	●	0	●

Adverse events reported after treating pkOA using bone marrow-derived cells

R	C	T	First author	Y	Cells	Treatment	Control	O
S10	3	a	Garay-Mendoza	2018	BMACBMAC	C	OA	auto
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto

QC	1	2	3	4	5	6	7	8
	●	●	●	●	●	●	●	

Adverse events reported after treating pkOA using adipose-derived cells

R	C	T	First author	Y	Cells	Treatment	Control	O
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S28	1	a	Lee	2019	ADSCs	C	S	auto

QC	1	2	3	4	5	6	7	8
	●	●	●	●	●		●	●

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Table S14 | Details of the sub-analyses performed in a meta-analysis by Han et al.[26].

Abbreviations: allo = allogeneic cells; auto = autologous cells; C = category of study as outlined in Table S2; O = origin of cells; QC = quality criteria (outlined in Table 1 in the main text; a point indicates that the corresponding quality criterion was fulfilled); R = reference number; T = type of study as outlined in Table S3; Y = year of publication. The abbreviations of the cell types and treatments are provided in Table S6.

VAS Pain score M6 bone marrow-derived cells

R	C	T	First author	Y	Cells	Treatment	Control	O
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S49	6	a	Vangsness	2014	BM-MSCs	C	S	allo
S49	6	a	Vangsness	2014	BM-MSCs	C	S	allo

QC	1	2	3	4	5	6	7	8
	●		●	●	●	●	●	

VAS Pain score M6 adipose-derived cells

R	C	T	First author	Y	Cells	Treatment	Control	O
S29	2	a	Lu	2019	ADSCs	C	HA	auto
S29	2	a	Lu	2019	ADSCs	C	HA	auto

QC	1	2	3	4	5	6	7	8
	●	●	●	●		●	●	

VAS Pain score M12 bone marrow-derived cells

R	C	T	First author	Y	Cells	Treatment	Control	O
S13	1	a	Gupta	2016	BM-MSCs	C	S	allo
S13	1	a	Gupta	2016	BM-MSCs	C	S	allo
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S49	6	a	Vangsness	2014	BM-MSCs	C	S	allo
S49	6	a	Vangsness	2014	BM-MSCs	C	S	allo
S51	2	a	Vega	2015	BM-MSCs	C	HA	allo

QC	1	2	3	4	5	6	7	8
	●		●	●	●		●	

VAS Pain score M12 adipose-derived cells

R	C	T	First author	Y	Cells	Treatment	Control	O
S23	4	c	Koh	2012	ADSCs	C + AD + PRP	AD + PRP	auto
S29	2	a	Lu	2019	ADSCs	C	HA	auto
S29	2	a	Lu	2019	ADSCs	C	HA	auto

QC	1	2	3	4	5	6	7	8
	●	●	●			●	●	

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VAS Pain score M24 bone marrow-derived cells

R	C	T	First author	Y	Cells	Treatment	Control	O
S49	6	a	Vangsness	2014	BM-MSCs	C	S	allo
S49	6	a	Vangsness	2014	BM-MSCs	C	S	allo

QC	1	2	3	4	5	6	7	8
	●		●	●	●	●	●	

VAS Pain score M24 adipose-derived cells

R	C	T	First author	Y	Cells	Treatment	Control	O
S23	4	c	Koh	2012	ADSCs	C + AD + PRP	AD + PRP	auto

QC	1	2	3	4	5	6	7	8
		●	●		●	●	●	●

WOMAC Total score at 6 months post treatment using bone marrow-derived cells

R	C	T	First author	Y	Cells	Treatment	Control	O
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto

QC	1	2	3	4	5	6	7	8
		●	●	●	●	●	●	

WOMAC Total score at 6 months post treatment using adipose-derived cells

R	C	T	First author	Y	Cells	Treatment	Control	O
S9	3	a	Freitag	2019	ADSCs	C	CM	auto
S9	3	a	Freitag	2019	ADSCs	C	CM	auto
S29	2	a	Lu	2019	ADSCs	C	HA	auto

QC	1	2	3	4	5	6	7	8
	●	●	●	●		●	●	

WOMAC Total score at 12 months post treatment using bone marrow-derived cells

R	C	T	First author	Y	Cells	Treatment	Control	O
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S51	2	a	Vega	2015	BM-MSCs	C	HA	allo

QC	1	2	3	4	5	6	7	8
	●	●	●	●				

WOMAC Total score at 12 months post treatment using adipose-derived cells

R	C	T	First author	Y	Cells	Treatment	Control	O
S9	3	a	Freitag	2019	ADSCs	C	CM	auto
S9	3	a	Freitag	2019	ADSCs	C	CM	auto
S29	2	a	Lu	2019	ADSCs	C	HA	auto

QC	1	2	3	4	5	6	7	8
	●	●	●	●		●	●	

Lysholm score at 12 months post treatment using bone marrow-derived cells

R	C	T	First author	Y	Cells	Treatment	Control	O
S49	6	a	Vangsness	2014	BM-MSCs	C	S	allo
S49	6	a	Vangsness	2014	BM-MSCs	C	S	allo
S53	4	a	Wong	2013	BM-MSCs	C + MF + HTO + HA	MF + HTO + HA	auto

QC	1	2	3	4	5	6	7	8
●		●	●	●	●			●

Lysholm score at 12 months post treatment using adipose-derived cells

R	C	T	First author	Y	Cells	Treatment	Control	O
S23	4	c	Koh	2012	ADSCs	C + AD + PRP	AD + PRP	auto

QC	1	2	3	4	5	6	7	8
		●	●		●	●	●	●

Lysholm score at 24 months post treatment using bone marrow-derived cells

R	C	T	First author	Y	Cells	Treatment	Control	O
S49	6	a	Vangsness	2014	BM-MSCs	C	S	allo
S49	6	a	Vangsness	2014	BM-MSCs	C	S	allo
S53	4	a	Wong	2013	BM-MSCs	C + MF + HTO + HA	MF + HTO + HA	auto

QC	1	2	3	4	5	6	7	8
	●		●	●	●	●		

Lysholm score at 24 months post treatment using adipose-derived cells

R	C	T	First author	Y	Cells	Treatment	Control	O
S23	4	c	Koh	2012	ADSCs	C + AD + PRP	AD + PRP	auto

QC	1	2	3	4	5	6	7	8
		●	●		●	●	●	●

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Tegner score at 12 months post treatment using bone marrow-derived cells

R	C	T	First author	Y	Cells	Treatment	Control	O
S53	4	a	Wong	2013	BM-MSCs	C + MF + HTO + HA	MF + HTO + HA	auto

QC	1	2	3	4	5	6	7	8
		●	●	●	●	●	●	●

Tegner score at 12 months post treatment using adipose-derived cells

R	C	T	First author	Y	Cells	Treatment	Control	O
S23	4	c	Koh	2012	ADSCs	C + AD + PRP	AD + PRP	auto

QC	1	2	3	4	5	6	7	8
		●	●		●	●	●	●

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Table S15 | Details of the sub-analyses performed in a meta-analysis by Kim et al.[17].

Abbreviations: allo = allogeneic cells; auto = autologous cells; C = category of study as outlined in Table S2; O = origin of cells; QC = quality criteria (outlined in Table 1 in the main text; a point indicates that the corresponding quality criterion was fulfilled); R = reference number; T = type of study as outlined in Table S3; Y = year of publication. The abbreviations of the cell types and treatments are provided in Table S6.

VAS Pain score

R	C	T	First author	Y	Cells	Treatment	Control	O
S51	2	a	Vega	2015	BM-MSCs	C	HA	allo
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S8	1	a	Emadedin	2018	BM-MSCs	C	S	auto

QC	1	2	3	4	5	6	7	8
	●	●	●	●			●	●

WOMAC Total score

R	C	T	First author	Y	Cells	Treatment	Control	O
S51	2	a	Vega	2015	BM-MSCs	C	HA	allo
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S8	1	a	Emadedin	2018	BM-MSCs	C	S	auto

QC	1	2	3	4	5	6	7	8
	●	●	●	●			●	●

WOMAC Pain score

R	C	T	First author	Y	Cells	Treatment	Control	O
S8	1	a	Emadedin	2018	BM-MSCs	C	S	auto
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S51	2	a	Vega	2015	BM-MSCs	C	HA	allo

QC	1	2	3	4	5	6	7	8
	●	●	●	●			●	●

WOMAC Function score

R	C	T	First author	Y	Cells	Treatment	Control	O
S8	1	a	Emadedin	2018	BM-MSCs	C	S	auto
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto

QC	1	2	3	4	5	6	7	8
	●	●	●	●	●		●	●

Whole-Organ Magnetic Resonance Imaging (WORMS) score

R	C	T	First author	Y	Cells	Treatment	Control	O
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo

QC	1	2	3	4	5	6	7	8
	●	●	●	●	●		●	●

Categorical evaluations of MRI data

R	C	T	First author	Y	Cells	Treatment	Control	O
S21	1	a	Khalifeh Soltani	2019	P-MSCs	C	S	allo
S26	1	a	Kuah	2018	ADSCs	C	S	allo

QC	1	2	3	4	5	6	7	8
	●	●	●	●	●	●	●	●

Cumulative pain scores (WOMAC and VAS): WOMAC

R	C	T	First author	Y	Cells	Treatment	Control	O
S51	2	a	Vega	2015	BM-MSCs	C	HA	allo
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S8	1	a	Emadedin	2018	BM-MSCs	C	S	auto

QC	1	2	3	4	5	6	7	8
	●	●	●	●			●	●

Cumulative pain scores (WOMAC and VAS): VAS

R	C	T	First author	Y	Cells	Treatment	Control	O
S51	2	a	Vega	2015	BM-MSCs	C	HA	allo
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S8	1	a	Emadedin	2018	BM-MSCs	C	S	auto
S26	1	a	Kuah	2018	ADSCs	C	S	allo

QC	1	2	3	4	5	6	7	8
	●	●	●	●			●	●

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Table S16 | Details of the sub-analyses performed in a meta-analysis by Ding et al.[25].

Abbreviations: allo = allogeneic cells; auto = autologous cells; C = category of study as outlined in Table S2; O = origin of cells; QC = quality criteria (outlined in Table 1 in the main text; a point indicates that the corresponding quality criterion was fulfilled); R = reference number; T = type of study as outlined in Table S3; Y = year of publication. The abbreviations of the cell types and treatments are provided in Table S6.

WOMAC Total score reported at 6 months post treatment using allogeneic cells

R	C	T	First author	Y	Cells	Treatment	Control	O
S31	2	a	Matas	2019	hUC-MSCs	C	HA	allo
S31	2	a	Matas	2019	hUC-MSCs	C	HA	allo
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S52	2	a	Wang	2016	hUC-MSCs	C	HA	allo
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S51	2	a	Vega	2015	BM-MSCs	C	HA	allo

QC	1	2	3	4	5	6	7	8
	●	●	●	●		●	●	

WOMAC Total score reported at 6 months post treatment using autologous cells

R	C	T	First author	Y	Cells	Treatment	Control	O
S29	2	a	Lu	2019	ADSCs	C	HA	auto
S9	3	a	Freitag	2019	ADSCs	C	CM	auto
S9	3	a	Freitag	2019	ADSCs	C	CM	auto
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S8	1	a	Emadedin	2018	BM-MSCs	C	S	auto

QC	1	2	3	4	5	6	7	8
	●	●	●	●		●	●	

KOOS score reported at 12 months post treatment using allogeneic cells

R	C	T	First author	Y	Cells	Treatment	Control	O
S22	1	a	Kim	2018	Ch-TGFß	C	S	allo

QC	1	2	3	4	5	6	7	8
		●	●	●	●	●	●	●

KOOS score reported at 12 months post treatment using autologous cells

R	C	T	First author	Y	Cells	Treatment	Control	O
S9	3	a	Freitag	2019	ADSCs	C	CM	auto
S9	3	a	Freitag	2019	ADSCs	C	CM	auto
S5	4	a	Bastos	2018	BM-MSCs	C + PRP	C	auto
S5	4	a	Bastos	2018	BM-MSCs	C + PRP	C	auto

QC	1	2	3	4	5	6	7	8
	●	●	●	●	●	●	●	

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VAS Pain score reported at 6 months post treatment using allogeneic cells

R	C	T	First author	Y	Cells	Treatment	Control	O
S31	2	a	Matas	2019	hUC-MSCs	C	HA	allo
S31	2	a	Matas	2019	hUC-MSCs	C	HA	allo
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S22	1	a	Kim	2018	Ch-TGFß	C	S	allo
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S51	2	a	Vega	2015	BM-MSCs	C	HA	allo

QC	1	2	3	4	5	6	7	8
	●	●	●	●		●	●	

VAS Pain score reported at 6 months post treatment using autologous cells

R	C	T	First author	Y	Cells	Treatment	Control	O
S29	2	a	Lu	2019	ADSCs	C	HA	auto
S9	3	a	Freitag	2019	ADSCs	C	CM	auto
S9	3	a	Freitag	2019	ADSCs	C	CM	auto
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S8	1	a	Emadedin	2018	BM-MSCs	C	S	auto

QC	1	2	3	4	5	6	7	8
	●	●	●	●		●	●	

Adverse events reported after treating pkOA using allogeneic cells

R	C	T	First author	Y	Cells	Treatment	Control	O
S31	2	a	Matas	2019	hUC-MSCs	C	HA	allo
S31	2	a	Matas	2019	hUC-MSCs	C	HA	allo
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S22	1	a	Kim	2018	Ch-TGFß	C	S	allo
S52	2	a	Wang	2016	hUC-MSCs	C	HA	allo
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S51	2	a	Vega	2015	BM-MSCs	C	HA	allo
S7	1	a	Cherian	2015	Ch-TGFß	C	S	allo

QC	1	2	3	4	5	6	7	8
	●	●	●	●		●	●	

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Adverse events reported after treating pkOA using autologous cells

R	C	T	First author	Y	Cells	Treatment	Control	O
S29	2	a	Lu	2019	ADSCs	C	HA	auto
S28	1	a	Lee	2019	ADSCs	C	S	auto
S9	3	a	Freitag	2019	ADSCs	C	CM	auto
S9	3	a	Freitag	2019	ADSCs	C	CM	auto
S8	1	a	Emadedin	2018	BM-MSCs	C	S	auto

QC	1	2	3	4	5	6	7	8
	●	●	●	●		●	●	●

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Table S17 | Details of the sub-analyses performed in a meta-analysis by Maheshwer et al.[29].

Abbreviations: allo = allogeneic cells; auto = autologous cells; C = category of study as outlined in Table S2; O = origin of cells; QC = quality criteria (outlined in Table 1 in the main text; a point indicates that the corresponding quality criterion was fulfilled); R = reference number; T = type of study as outlined in Table S3; Y = year of publication. The abbreviations of the cell types and treatments are provided in Table S6.

VAS Pain score

R	C	T	First author	Y	Cells	Treatment	Control	O
S23	4	c	Koh	2012	ADSCs	C + AD + PRP	AD + PRP	auto
S25	4	a	Koh	2014	ADRCs	C + AD + HTO + PRP	AD + HTO + PRP	auto
S1	6	a	Akgun	2015	S-MSCs	C in S + AD	MACI	auto
S51	2	a	Vega	2015	BM-MSCs	C	HA	allo
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S29	2	a	Lu	2019	ADSCs	C	HA	auto
S29	2	a	Lu	2019	ADSCs	C	HA	auto

QC	1	2	3	4	5	6	7	8
	●	●	●					

VAS Pain score after treating pkOA using stem cells

R	C	T	First author	Y	Cells	Treatment	Control	O
S51	2	a	Vega	2015	BM-MSCs	C	HA	allo
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S29	2	a	Lu	2019	ADSCs	C	HA	auto
S29	2	a	Lu	2019	ADSCs	C	HA	auto

QC	1	2	3	4	5	6	7	8
	●	●	●	●			●	

VAS Pain score after treating pkOA with stem cells in conjunction with surgery

R	C	T	First author	Y	Cells	Treatment	Control	O
S23	4	c	Koh	2012	ADSCs	C + AD + PRP	AD + PRP	auto
S25	4	a	Koh	2014	ADRCs	C + AD + HTO + PRP	AD + HTO + PRP	auto
S1	6	a	Akgun	2015	S-MSCs	C in S + AD	MACI	auto

QC	1	2	3	4	5	6	7	8
	●	●	●			●	●	●

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WOMAC Total score

R	C	T	First author	Y	Cells	Treatment	Control	O
S51	2	a	Vega	2015	BM-MSCs	C	HA	allo
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo

QC	1	2	3	4	5	6	7	8
	●	●	●	●		●	●	

IKDC scoore

R	C	T	First author	Y	Cells	Treatment	Control	O
S22	4	c	Kim	2018	ADRCs	C + AD + HTO	AD + HTO	auto

QC	1	2	3	4	5	6	7	8
		●	●		●	●	●	●

Lysholm score

R	C	T	First author	Y	Cells	Treatment	Control	O
S23	4	c	Koh	2012	ADSCs	C + AD + PRP	AD + PRP	auto
S25	4	a	Koh	2014	ADRCs	C + AD + HTO + PRP	AD + HTO + PRP	auto

QC	1	2	3	4	5	6	7	8
	●	●	●		●	●		●

KOOS score

R	C	T	First author	Y	Cells	Treatment	Control	O
S1	6	a	Akgun	2015	S-MSCs	C in S + AD	MACI	auto

QC	1	2	3	4	5	6	7	8
		●	●	●		●	●	●

Physical function after treating pkOA using stem cells

R	C	T	First author	Y	Cells	Treatment	Control	O
S51	2	a	Vega	2015	BM-MSCs	C	HA	allo
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S29	2	a	Lu	2019	ADSCs	C	HA	auto

QC	1	2	3	4	5	6	7	8
	●	●	●	●			●	

Physical function after treating pkOA with stem cells in conjunction with surgery

R	C	T	First author	Y	Cells	Treatment	Control	O
S23	4	c	Koh	2012	ADSCs	C + AD + PRP	AD + PRP	auto
S1	6	a	Akgun	2015	S-MSCs	C in S + AD	MACI	auto
S22	4	c	Kim	2018	ADRCs	C + AD + HTO	AD + HTO	auto
S25	4	a	Koh	2014	ADRCs	C + AD + HTO + PRP	AD + HTO + PRP	auto

QC	1	2	3	4	5	6	7	8
	●	●	●			●		●

Cartilage volume

R	C	T	First author	Y	Cells	Treatment	Control	O
S28	1	a	Lee	2019	ADSCs	C	S	auto
S29	2	a	Lu	2019	ADSCs	C	HA	auto
S29	2	a	Lu	2019	ADSCs	C	HA	auto
S29	2	a	Lu	2019	ADSCs	C	HA	auto
S29	2	a	Lu	2019	ADSCs	C	HA	auto

QC	1	2	3	4	5	6	7	8
	●	●	●	●		●	●	

Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART) score (cartilage quality)

R	C	T	First author	Y	Cells	Treatment	Control	O
S15	6	a	Hashimoto	2019	BM-MSCs	C + MF	MF	auto

QC	1	2	3	4	5	6	7	8
		●	●	●	●	●	●	●

Poor cartilage index

R	C	T	First author	Y	Cells	Treatment	Control	O
S51	2	a	Vega	2015	BM-MSCs	C	HA	allo

QC	1	2	3	4	5	6	7	8
		●	●	●		●	●	●

Whole-Organ Magnetic Resonance Imaging (WORMS) score

R	C	T	First author	Y	Cells	Treatment	Control	O
S13	4	a	Gupta	2016	BM-MSCs	C	S	allo
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo
S13	4	a	Gupta	2016	BM-MSCs	C + HA	S + HA	allo

QC	1	2	3	4	5	6	7	8
	●	●	●	●	●	●	●	

Table S18 | Details of the sub-analyses performed in a meta-analysis by Dai et al.[24].

Abbreviations: allo = allogeneic cells; auto = autologous cells; C = category of study as outlined in Table S2; O = origin of cells; QC = quality criteria (outlined in Table 1 in the main text; a point indicates that the corresponding quality criterion was fulfilled); R = reference number; T = type of study as outlined in Table S3; Y = year of publication. The abbreviations of the cell types and treatments are provided in Table S6.

VAS Pain score MSCs vs control

R	C	T	First author	Y	Cells	Treatment	Control	O
S8	1	a	Emadedin	2018	BM-MSCs	C	S	auto
S13	1	a	Gupta	2016	BM-MSCs	C	S	allo
S16	4	b	Hong	2019	ADRCs	C + AD	HA + AD	auto
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S29	2	a	Lu	2019	ADSCs	C	HA	auto
S31	2	a	Matas	2019	hUC-MSCs	C	HA	allo
S40	4	b	Shapiro	2019	BMACBMAC	C + PPP	S	auto
S51	2	a	Vega	2015	BM-MSCs	C	HA	allo

QC	1	2	3	4	5	6	7	8
	●	●	●					●

VAS Pain score MSC vs placebo

R	C	T	First author	Y	Cells	Treatment	Control	O
S8	1	a	Emadedin	2018	BM-MSCs	C	S	auto
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S40	4	b	Shapiro	2019	BMACBMAC	C + PPP	S	auto

QC	1	2	3	4	5	6	7	8
	●	●	●					●

VAS Pain score MSC vs HA

R	C	T	First author	Y	Cells	Treatment	Control	O
S13	1	a	Gupta	2016	BM-MSCs	C	S	allo
S16	4	b	Hong	2019	ADRCs	C + AD	HA + AD	auto
S29	2	a	Lu	2019	ADSCs	C	HA	auto
S31	2	a	Matas	2019	hUC-MSCs	C	HA	allo
S51	2	a	Vega	2015	BM-MSCs	C	HA	allo

QC	1	2	3	4	5	6	7	8
	●	●	●					●

WOMAC Total score MSCs vs control

R	C	T	First author	Y	Cells	Treatment	Control	O
S8	1	a	Emadedin	2018	BM-MSCs	C	S	auto
S9	3	a	Freitag	2019	ADSCs	C	CM	auto
S11	1	a	Garza	2020	ADRCs	C	RS	auto
S13	1	a	Gupta	2016	BM-MSCs	C	S	allo
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S29	2	a	Lu	2019	ADSCs	C	HA	auto
S31	2	a	Matas	2019	hUC-MSCs	C	HA	allo
S51	2	a	Vega	2015	BM-MSCs	C	HA	allo

QC	1	2	3	4	5	6	7	8
	●	●	●	●				●

WOMAC Total score MSC vs placebo

R	C	T	First author	Y	Cells	Treatment	Control	O
S8	1	a	Emadedin	2018	BM-MSCs	C	S	auto
S9	3	a	Freitag	2019	ADSCs	C	CM	auto
S11	1	a	Garza	2020	ADRCs	C	RS	auto
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto

QC	1	2	3	4	5	6	7	8
	●	●	●	●	●	●		●

WOMAC Total score MSC vs HA

R	C	T	First author	Y	Cells	Treatment	Control	O
S13	1	a	Gupta	2016	BM-MSCs	C	S	allo
S29	2	a	Lu	2019	ADSCs	C	HA	auto
S31	2	a	Matas	2019	hUC-MSCs	C	HA	allo
S51	2	a	Vega	2015	BM-MSCs	C	HA	allo

QC	1	2	3	4	5	6	7	8
	●	●	●	●			●	●

VAS Pain score Adipose-derived MSCs

R	C	T	First author	Y	Cells	Treatment	Control	O
S16	4	b	Hong	2019	ADRCs	C + AD	HA + AD	auto
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S29	2	a	Lu	2019	ADSCs	C	HA	auto

QC	1	2	3	4	5	6	7	8
	●	●	●					●

VAS Pain score Bone marrow-derived MSCs

R	C	T	First author	Y	Cells	Treatment	Control	O
S8	1	a	Emadedin	2018	BM-MSCs	C	S	auto
S13	1	a	Gupta	2016	BM-MSCs	C	S	allo
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S40	4	b	Shapiro	2019	BMACBMAC	C + PPP	S	auto
S51	2	a	Vega	2015	BM-MSCs	C	HA	allo

QC	1	2	3	4	5	6	7	8
	●	●	●					●

VAS Pain score Umbilical cord-derived MSCs

R	C	T	First author	Y	Cells	Treatment	Control	O
S31	2	a	Matas	2019	hUC-MSCs	C	HA	allo

QC	1	2	3	4	5	6	7	8
		●	●	●		●	●	●

WOMAC Total score Adipose-derived MSCs

R	C	T	First author	Y	Cells	Treatment	Control	O
S9	3	a	Freitag	2019	ADSCs	C	CM	auto
S11	1	a	Garza	2020	ADRCs	C	RS	auto
S29	2	a	Lu	2019	ADSCs	C	HA	auto

QC	1	2	3	4	5	6	7	8
	●	●	●	●		●		●

WOMAC Total score Bone marrow-derived MSCs

R	C	T	First author	Y	Cells	Treatment	Control	O
S8	1	a	Emadedin	2018	BM-MSCs	C	S	auto
S13	1	a	Gupta	2016	BM-MSCs	C	S	allo
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S51	2	a	Vega	2015	BM-MSCs	C	HA	allo

QC	1	2	3	4	5	6	7	8
	●	●	●	●			●	●

WOMAC Total score Umbilical cord-derived MSCs

R	C	T	First author	Y	Cells	Treatment	Control	O
S31	2	a	Matas	2019	hUC-MSCs	C	HA	allo

QC	1	2	3	4	5	6	7	8
		●	●	●		●	●	●

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VAS Pain score Cultured cells

R	C	T	First author	Y	Cells	Treatment	Control	O
S8	1	a	Emadedin	2018	BM-MSCs	C	S	auto
S13	1	a	Gupta	2016	BM-MSCs	C	S	allo
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S29	2	a	Lu	2019	ADSCs	C	HA	auto
S31	2	a	Matas	2019	hUC-MSCs	C	HA	allo
S51	2	a	Vega	2015	BM-MSCs	C	HA	allo

QC	1	2	3	4	5	6	7	8
	●	●	●	●			●	●

VAS Pain score Uncultured cells

R	C	T	First author	Y	Cells	Treatment	Control	O
S16	4	b	Hong	2019	ADRCs	C + AD	HA + AD	auto
S40	4	b	Shapiro	2019	BMACBMAC	C + PPP	S	auto

QC	1	2	3	4	5	6	7	8
	●	●	●			●	●	●

WOMAC Total score Cultured cells

R	C	T	First author	Y	Cells	Treatment	Control	O
S8	1	a	Emadedin	2018	BM-MSCs	C	S	auto
S9	3	a	Freitag	2019	ADSCs	C	CM	auto
S13	1	a	Gupta	2016	BM-MSCs	C	S	allo
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S29	2	a	Lu	2019	ADSCs	C	HA	auto
S31	2	a	Matas	2019	hUC-MSCs	C	HA	allo
S51	2	a	Vega	2015	BM-MSCs	C	HA	allo

QC	1	2	3	4	5	6	7	8
	●	●	●	●			●	●

WOMAC Total score Uncultured cells

R	C	T	First author	Y	Cells	Treatment	Control	O
S11	1	a	Garza	2020	ADRCs	C	RS	auto

QC	1	2	3	4	5	6	7	8
		●	●	●	●	●	●	●

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VAS Pain score Autologous cells

R	C	T	First author	Y	Cells	Treatment	Control	O
S8	1	a	Emadedin	2018	BM-MSCs	C	S	auto
S16	4	b	Hong	2019	ADRCs	C + AD	HA + AD	auto
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S29	2	a	Lu	2019	ADSCs	C	HA	auto
S40	4	b	Shapiro	2019	BMACBMAC	C + PPP	S	auto

QC	1	2	3	4	5	6	7	8
	●	●	●			●		●

VAS Pain score Allogeneic cells

R	C	T	First author	Y	Cells	Treatment	Control	O
S13	1	a	Gupta	2016	BM-MSCs	C	S	allo
S26	1	a	Kuah	2018	ADSCs	C	S	allo
S31	2	a	Matas	2019	hUC-MSCs	C	HA	allo
S51	2	a	Vega	2015	BM-MSCs	C	HA	allo

QC	1	2	3	4	5	6	7	8
	●	●	●	●		●	●	●

WOMAC Total score Autologous cells

R	C	T	First author	Y	Cells	Treatment	Control	O
S8	1	a	Emadedin	2018	BM-MSCs	C	S	auto
S9	3	a	Freitag	2019	ADSCs	C	CM	auto
S11	1	a	Garza	2020	ADRCs	C	RS	auto
S27	4	a	Lamo-Espinosa	2016	BM-MSCs	C + HA	HA	auto
S29	2	a	Lu	2019	ADSCs	C	HA	auto

QC	1	2	3	4	5	6	7	8
	●	●	●	●		●		●

WOMAC Total score Allogeneic cells

R	C	T	First author	Y	Cells	Treatment	Control	O
S13	1	a	Gupta	2016	BM-MSCs	C	S	allo
S31	2	a	Matas	2019	hUC-MSCs	C	HA	allo
S51	2	a	Vega	2015	BM-MSCs	C	HA	allo

QC	1	2	3	4	5	6	7	8
	●	●	●	●		●	●	●

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Table S19 | Details of studies that were identified during an evidence-based, systematic review of the literature according to the PRISMA guidelines[14] performed on August 07, 2021 in order to examine studies on treatment of primary knee osteoarthritis with stem cells.

Abbreviations: AD = arthroscopic debridement; ADRCs = adipose-derived regenerative cells; ADSCs = adipose-derived stem cells (obtained by culturing ADRCs); AlCh = allogeneic cartilage; allo = allogeneic; AM = arthroscopic repair of meniscus; auto = autologous; AMIC = autologous matrix-induced chondrogenesis; AP = autologous periosteum; AuCh = autologous chondrocytes; BMA = bone marrow aspirate; BMAC = bone marrow aspirate concentrate; BM-MSCs = bone marrow-derived mesenchymal stem cells; Ca, category of study as defined in Table S2; Ccs = subchondral application of cells; Ce = cell type; CF = centrifuged fat; Ch-TGFß = chondrocytes overexpressing transforming growth factor beta; CLL = centrifuged liposuction liquid; CM = conservative management; Cs = chondrocytes; CS = corticosteroid; CSCs = cartilage stem cells; Cu = culturing of cells; DFO = distal femoral osteotomy; FA = first author; FF = filtrated fat; GF = growth factor; HA = hayluronic acid; HTO = high tibial osteotomy; hUC-MSCs = human umbilical cord-derived MSCs; hUCB-MSCs = human umbilical cord blood-derived MSCs; MACI = matrix-induced autologous chondrocyte implant; MF = microfracture; MFF = micro-fragmented fat (from liposuction); N = number of patients in the treatment group; O = origin of cells; OA = oral acetaminophen; pBSCs = activated peripheral blood stem cells; PL = platelet lysate; P-MSCs = placental MSCs; PRP = platelet rich plasma; RS = Ringer solution; S = scaffold; Sa = saline; S-MSCs = matrix-induced MSCs from synovia; SR = surgical repair; R = reference; T = type of study as defined in Table S3; TPA = total knee arthroplasty (internal control); Y = year of publication;

Remark: a, in a study of Centeno et al. (2021) a combination of autologous BMAC + PRP + PL was administered into the knee joint and the subchondral bone (treatment group), or into the knee joint alone (control group), respectively.

R	Ca	T	FA	Y	Ce	O	Treatment	N	Control	Cu
S7	I	a	Cherian	2015	Ch-TGFß	allo	C	50	Sa	Yes
S13	I	a	Gupta	2016	BM-MSCs	allo	C + HA	40	C or S	Yes
S8	I	a	Emadedin	2018	BM-MSCs	auto	C	19	Sa	Yes
S22	I	a	Kim	2018	Ch-TGFß	allo	C	78	Sa	Yes
S26	I	a	Kuah	2018	ADSCs	allo	C	16	Sa	Yes
S21	I	a	Khalifeh Soltani	2019	P-MSCs	allo	C	10	Sa	Yes
S28	I	a	Lee	2019	ADSCs	auto	C	12	Sa	Yes
S11	I	a	Garza	2020	ADRCs	auto	C	26	RS	No
S51	II	a	Vega	2015	BM-MSCs	allo	C	15	HA	Yes
S52	II	a	Wang	2016	hUC-MSCs	allo	C	18	HA	Yes
S12	II	a	Goncars	2017	BMAC	auto	C	28	HA	No
S29	II	a	Lu	2019	ADSCs	auto	C	26	HA	Yes
S31	II	a	Matas	2019	hUC-MSCs	allo	C	18	HA	Yes
S3	II	a	Anz	2020	BMAC	auto	C	45	PRP	No
S80	II	a	Dallo	2021	MFF	auto	C	40	PRP+HA	No
S121	II	d	Kim	2020	ADRCs	auto	C	30	HA	No

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Table S19 (cont.)

R	Ca	T	FA	Y	Ce	O	Treatment	N	Control	Cu
S10	III	a	Garay-Mendoza	2018	BMAC	auto	C	61	OA	No
S44	III	a	Song	2018	ADSCs	auto	C	18	C	Yes
S9	III	a	Freitag	2019	ADSCs	auto	C	20	CM	Yes
S187	III	a	Zhao	2019	ADSCs	allo	C	18	C	Yes
S4	III	a	Bastos	2020	BM-MSCs	auto	C	16	C + PRP +CS	Yes
S135	III	a	Lu	2020	ADSCs	allo	C	22	C	Yes
S105	III	b	Hernigou	2018	BMAC	auto	C	30	TPA	No
S106	III	b	Hernigou	2020	BMAC	auto	C	60	Csc	No
S107	III	b	Hernigou	2020	BMAC	auto	C	140	TPA	No
S20	III	c	Jo	2014	ADSCs	auto	C	18	C	Yes
S36	III	c	Pers	2016	ADSCs	auto	C	18	C	Yes
S19	III	c	Jo	2017	ADSCs	auto	C	18	C	Yes
S35	III	c	Pers	2018	ADSCs	auto	C	18	C	Yes
S76	III	c	Chahal	2019	ADSCs	auto	C	12	C	Yes
S89	III	c	Estrada	2020	ADRCs	auto	C	33	BMAC + PRP	No
S112	III	c	Kazemian	2020	BM-MSCs	auto	C	20	Not described	Yes
S147	III	c	Papalia	2020	MFF	auto	C	8	CF or FF	No
S60	III	c	Bistolfi	2021	MFF	auto	C	27	CF	No
S32	III	d	Mautner	2019	MFF	auto	C	23	BMAC	No
S54	III	d	Yokota	2019	ADRCs	auto	C	38	C	No
S132	III	d	Li	2020	BM-MSCs	auto	C	40	AD + HA	Yes
S168	III	d	Simunec	2020	ADRCs	auto	C	6	C + PRP	No
S50	IV	a	Varma	2010	BM-MSCs	auto	C + AD	25	AD	Yes
S53	IV	a	Wong	2013	BM-MSCs	auto	C + MF + HTO + HA	28	HA + HTO + MF	Yes
S25	IV	a	Koh	2014	ADRCs	auto	C + AD + HTO + PRP	21	PRP + AD + HTO	No
S27	IV	a	Lamo-Espinosa	2016	BM-MSCs	auto	C + HA	10	HA	Yes
S177	IV	a	Turajane	2017	pBSCs	auto	C + AD + MF	20	HA	No
S5	IV	a	Bastos	2018	BM-MSCs	auto	C + PRP	9	C	Yes
S56	IV	a	Zhang	2018	ADSCs	auto	C + HA	36	C	Yes
S128	IV	a	Lamo-Espinosa	2018	BM-MSCs	auto	C + HA	10	HA	Yes
S149	IV	a	Peretti	2018	MFF	auto	C + AD	20	AD	No
S129	IV	a	Lamo-Espinosa	2020	BM-MSCs	auto	C + PRP	30	PRP	Yes
S152	IV	a	Qiao	2020	ADSCs	auto	C + AD + MF + HA	10	MF or MF + HA	Yes
S154	IV	a	Ruane	2021	BMAC	auto	C + PRP	17	HA	No
S41	IV	b	Shapiro	2017	BMAC	auto	C + PPP	25	S	No
S16	IV	b	Hong	2019	ADRCs	auto	C + AD	16	HA + AD	No
S40	IV	b	Shapiro	2019	BMAC	auto	C + PPP	25	S	No

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Table S19 (cont.)

R	Ca	T	FA	Y	Ce	O	Treatment	N	Control	Cu
S23	IV	c	Koh	2012	ADSCs	auto	C + AD + PRP	25	AD + PRP	?
S119	IV	c	Kim	2015	ADRCs	auto	C + AD + PRP	20	C in S + AD	No
S33	IV	c	Nguyen	2017	ADRCs	auto	C + AD + MF + PRP	15	AD + MF	No
S118	IV	c	Kim	2018	ADRCs	auto	C + AD + HTO	50	HTO	No
S47	IV	c	Tran	2019	ADRCs	auto	C + AD + MF	18	AD + MF	No
S86	IV	c	Ehlers	2020	ADRCs	auto	C + PRP	8	PRP	No
S72	IV	d	Centeno	2014	BMAC	auto	C + adipose graft	840	C	No
S116	IV	d	Kim	2015	ADRCs	auto	C in S + AD	17	C + AD	No
S175	IV	d	Srinivas	2015	BMAC	auto	C + PRP +Co	65	Co	No
S130	IV	d	Lee	2021	BMAC	auto	C + MF + HTO	74	hUCB-MSCs	No
S71	IV	d	Centeno	2021	BMAC	auto	BMAC + PRP + PL[a]	80	BMAC + PRP +PL[a]	
S136	IV	d	Magnanelli	2021	MFF	auto	C + HTO	42	HTO	No
S81	V	e	Davatchi	2011	BM-MSCs	auto	C	4	None	Yes
S146	V	e	Pak	2011	ADRCs	auto	C + PRP + HA	2	None	No
S87	V	e	Emadedin	2012	BM-MSCs	auto	C	6	None	Yes
S102	V	e	Hauser	2013	BMA	auto	C	3	None	No
S24	V	e	Koh	2013	ADRCs	auto	C + PRP + HA	33	None	No
S34	V	e	Orozco	2013	BM-MSCs	auto	C	12	None	Yes
S178	V	e	Turajane	2013	pBSCs	auto	C + MF + GF + HA	4	None	No
S58	V	e	Ahmad	2014	pBSCs	auto	C	10	None	No
S66	V	e	Bui	2014	ADRCs	auto	C + PRP	23	None	No
S123	V	e	Koh	2014	ADRCs	auto	C + AD	37	None	No
S144	V	e	Orozco	2014	BM-MSCs	auto	C	12	None	Yes
S73	V	e	Centeno	2015	BMAC	auto	C	373	None	No
S88	V	e	Emadedin	2015	BM-MSCs	auto	C	6	None	Yes
S96	V	e	Gibbs	2015	ADRCs	auto	C + PRP	4	None	No
S114	V	e	Kim	2015	ADRCs	auto	C in S + AD	55	None	No
S124	V	e	Koh	2015	ADRCs	auto	C +AL	30	None	No
S82	V	e	Davatchi	2016	BM-MSCs	auto	C	4	None	Yes
S90	V	e	Fodor	2016	ADRCs	auto	C	6	None	No
S115	V	e	Kim	2016	ADRCs	auto	C in S + AD	20	None	No
S145	V	e	Pak	2016	ADRCs	auto	C + PRP + HA	3	None	No
S159	V	e	Sampson	2016	BMAC	auto	C + PRP	125	None	No
S43	V	e	Soler	2016	BM-MSCs	auto	C	15	None	Yes
S2	V	e	Al-Najar	2017	BM-MSCs	auto	C	13	None	Yes
S18	V	e	Hudetz	2017	MFF	auto	C	17	None	No
S148	V	e	Park	2017	hUCB-MSCs	allo	C + MF	6	None	Yes
S150	V	e	Pintat	2017	ADRCs	auto	C + PRP	19	None	?

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Table S19 (cont.)

R	Ca	T	FA	Y	Ce	O	Treatment	N	Control	Cu
S155	V	e	Russo	2017	MFF	auto	C	30	None	No
S170	V	e	Smyshlyaev	2017	ADRCs	auto	C	28	None	No
S55	V	e	Yokota	2017	ADRCs	auto	C	13	None	No
S69	V	e	Cattaneo	2018	MFF	auto	C	38	None	No
S70	V	e	Cavallo	2018	BMAC	auto	C + AD + PRP	24	None	No
S153	V	e	Rodriguez-Fontan	2018	BMAC	auto	C	10	None	No
S156	V	e	Russo	2018	MFF	auto	C	30	None	No
S42	V	e	Shaw	2018	BMAC	auto	C	15	None	No
S45	V	e	Spasovski	2018	ADSCs	auto	C	9	None	Yes
S46	V	e	Themistocleous	2018	BMAC	auto	C	233	None	No
S62	V	e	Borić	2019	MFF	auto	C	17	None	No
S101	V	e	Goncars	2019	BMAC	auto	C	32	None	No
S17	V	e	Hudetz	2019	MFF	auto	C	20	None	No
S141	V	e	Monckeberg	2019	pBSCs	auto	C + PRP	20	None	Yes
S143	V	e	Onoi	2019	ADRCs	auto	C	2	None	No
S37	V	e	Roato	2019	CLL	auto	C + AD	20	None	No
S39	V	e	Schiavone Panni	2019	MFF	auto	C + AD	52	None	No
S171	V	e	Song	2019	hUCB-MSCs	allo	C + DFO	2	None	Yes
S183	V	e	Wang	2019	BM-MSCs	auto	C + chondrocytes	2	None	Yes
S79	V	e	Colberg	2020	BMAC	auto	C	10	None	No
S84	V	e	Dilogo	2020	hUC-MSCs	allo	C	39	None	Yes
S85	V	e	Dulic	2020	BMAC	auto	C	111	None	No
S95	V	e	Freitag	2020	ADSCs	auto	C + AD	27	None	Yes
S104	V	e	Heidari	2020	MFF	auto	C	110	None	No
S108	V	e	Higuchi	2020	ADSCs	auto	C	34	None	Yes
S113	V	e	Kim	2020	BMAC	auto	C	25	None	No
S120	V	e	Kim	2020	ADRCs	auto	C in S	467	None	No
S127	V	e	Lapuente	2020	ADRCs	auto	C	50	None	No
S139	V	e	Mehling	2020	ADRCs	auto	C + PRP	241	None	No
S151	V	e	Prodromos	2020	MFF	auto	C + PRP	42	None	No
S172	V	e	Song	2020	hUCB-MSCs	allo	C + AD + MF + HA	128	None	Yes
S173	V	e	Song	2020	hUCB-MSCs	allo	C + MF + HTO + HA	25	None	Yes
S174	V	e	Song	2020	hUCB-MSCs	allo	C + MF + HTO + HA	25	None	Yes
S176	V	e	Toan	2020	BM-MSCs	auto	C + AD	46	None	?
S48	V	e	Tsubosaka	2020	ADRCs	auto	C	57	None	No
S180	V	e	Varady	2020	BMAC	auto	C	17	None	No
S184	V	e	Wells	2020	BMAC	auto	C	11	None	No
S59	V	e	Bakowski	2021	MFF	auto	C	59	None	No

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Table S19 (cont.)

R	Ca	T	FA	Y	Ce	O	Treatment	N	Control	Cu
S61	V	e	Borg	2021	MFF	auto	C	456	None	No
S67	V	e	Burnham	2021	BMAC	auto	C	112	None	No
S68	V	e	Caforio	2021	MFF	auto	C + AD	30	None	No
S103	V	e	Heidari	2021	MFF	auto	C	344	None	No
S122	V	e	Kim	2021	ADRCs	auto	C + AD + HTO	75	None	No
S137	V	e	Malanga	2021	MFF	auto	C	20	None	No
S160	V	e	Santoprete	2021	ADRCs	auto	C	84	None	No
S163	V	e	Sekiya	2021	S-MSCs	auto	C	8	None	Yes
S179	V	e	Van Genechten	2021	MFF	auto	C	64	None	No
S74	V	f	Centeno	2008	BM-MSCs	auto	C	1	None	Yes
S75	V	f	Centeno	2008	BM-MSCs	auto	C	1	None	Yes
S140	V	f	Mehrabani	2016	BM-MSCs	auto	C	1	None	Yes
S63	V	f	Bright	2018	ADRCs	auto	C	1	None	No
S92	V	f	Freitag	2019	ADSCs	auto	C + AD + HTO	1	None	Yes
S182	VI	a	Wakitani	2002	BM-MSCs	auto	C + AD + HTO + aP	12	HTO	Yes
S38	VI	a	Saw	2013	pBSCs	auto	C + MF + HA	25	HA	No
S1	VI	a	Akgun	2015	S-MSCs	auto	C in S + AD	7	MACI	Yes
S125	IV	a	Koh	2016	ADRCs	auto	C in S + MF	20	MF	No
S165	VI	a	Shadmanfar	2018	BM-MSCs	auto	C	15	Placebo	Yes
S83	VI	a	de Girolamo	2019	BMAC	auto	C + AMIC	12	AMIC	No
S15	VI	a	Hashimoto	2019	BM-MSCs	auto	C + MF	7	MF	Yes
S142	VI	a	Olivos-Meza	2019	pBSCs	auto	C in S	17	Sa	Yes
S117	VI	a	Kim	2020	ADRCs	auto	C + AD + HTO	40	C + AD + HTO + Aca	No
S133	VI	a	Lim	2021	hUCB-MSCs	allo	C + AD + MF	73	MF	Yes
S162	VI	a	Saw	2021	pBSCs	auto	C + MF + HA	35	HA	No
S97	VI	c	Gobbi	2015	BMAC	auto	C in S + AD	19	MACI	No
S100	VI	c	Gobbi	2016	BMAC	auto	C in S	27	MF	No
S138	VI	c	Martinčič	2020	BMAC	auto	C in S	9	autoCh	No
S157	VI	d	Ryu	2020	BMAC	auto	C + AD	52	hUC-MSCs	No
S111	VI	e	Kasemkijwattana	2011	BM-MSCs	auto	C in S	2	None	Yes
S169	VI	e	Skowroński	2012	pBSCs	auto	C in S + AD	52	None	No
S65	VI	e	Buda	2013	BMAC	auto	C in S + AD	20	None	No
S98	VI	e	Gobbi	2014	BMAC	auto	C in S + AD	25	None	No
S186	VI	e	Zhang	2014	MACI	auto	C in S + AD	15	None	Yes
S109	VI	e	Jiang	2016	CSCs	auto	C in S + AD	15	None	Yes
S158	VI	e	Sadlik	2017	hUC-MSCs	allo	C in S	?	None	Yes
S185	VI	e	Whitehouse	2017	BM-MSCs	auto	C in S	5	None	Yes
S110	VI	e	Kamei	2018	BM-MSCs	auto	C	5	None	Yes

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Table S19 (cont.)

R	Ca	T	FA	Y	Ce	O	Treatment	N	Control	Cu
S166	VI	e	Shetty	2018	BMAC	auto	C + AD + MF	60	None	No
S167	VI	e	Shimomura	2018	S-MSCs	auto	C	5	None	Yes
S99	VI	e	Gobbi	2019	BMAC	auto	C in S + AD	23	None	No
S164	VI	e	Sekiya	2019	S-MSCs	auto	C + SR	6	None	Yes
S78	VI	e	Ciemniewska-Gorzela	2020	BMAC	auto	C in S + AM	54	None	No
S94	VI	e	Freitag	2020	ADSCs	auto	C + AD	8	None	Yes
S181	VI	e	Veber	2020	BMAC	auto	C in S	15	None	No
S77	VI	e	Chung	2021	hUCB-MSCs	allo	C + AD + HTO	93	None	Yes
S134	VI	e	Liu	2021	Cs/CPs	auto	C in S + AD	12	None	Yes
S161	VI	e	Saris	2021	BM-MSCs	allo	C + AD	35	None	Yes
S57	VI	f	Adachi	2005	BM-MSCs	auto	C in S	1	None	Yes
S126	VI	f	Kuroda	2007	BM-MSCs	auto	C in S	1	None	Yes
S64	VI	f	Broyles	2017	BMAC	auto	C + PRP + HA	1	None	No
S93	VI	f	Freitag	2017	ADSCs	auto	C	1	None	Yes
S91	VI	f	Freitag	2017	ADSCs	auto	C	1	None	Yes
S131	VI	f	Leigheb	2017	Cs	auto	C in S	1	None	Yes

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Table S20 | Categories of studies on treatment of primary knee osteoarthritis (pkOA) with stem cells that were identified during an evidence-based, systematic review of the literature according to the PRISMA guidelines[14] performed on August 07, 2021 (summarized in Table S19).

Abbreviations: Ca = category; CS = corticosteroid; N = number of studies; HA = hyaluronic acid; i.a. = intra-articular; PRP = platelet rich plasma.

Ca	N	Description
I	8	Treatment of pkOA with i.a. injection of stem cells as the sole treatment (not considering rehabilitation), compared with i.a. injection of saline or sham treatment as control.
II	8	Treatment of pkOA with i.a. injection of stem cells as the sole treatment (not considering rehabilitation), compared with i.a. injection of respectively PRP, CS or HA as control.
III	22	Treatment of pkOA with i.a. injection of stem cells as the sole treatment (not considering rehabilitation), compared with other treatments than those in Categories I and II as control.
IV	27	Treatment of pkOA with combinations of stem cells and other modalities, compared with sham treatment or other treatments as control.
V	78	Treatment of pkOA with combinations of stem cells with or without other modalities, without control group (case series or case reports).
VI	40	Treatment of focal chondral, osteochondral or meniscal chondral lesions with stem cells as the sole treatment (not considering rehabilitation) or combinations of stem cells and other modalities, with or without other treatments as control.
Sum	183	

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Table S21 | Types of studies on treatment of primary knee osteoarthritis (pkOA) with stem cells that were identified during an evidence-based, systematic review of the literature according to the PRISMA guidelines[14] performed on August 07, 2021.

Abbreviations: Ca = category; N_{all} = number of studies among all studies listed in Table S19; N_{pkOA} = number of studies among those studies listed in Table S19 that addressed pkOA.

Ca	N_{all}	N_{pkOA}	Description
a	44	33	Randomized controlled trials (RCTs)
b	6	6	RCTs with the contralateral knee as internal control
c	18	15	Prospective cohort studies
d	12	11	Retrospective cohort studies
e	92	73	Case series with more than one subject
f	11	5	Case reports with only one subject
Sum	183	143	

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Table S22 | Types of stem cells used in studies on treatment of primary knee osteoarthritis pkOA with stem cells that were identified during an evidence-based, systematic review of the literature according to the PRISMA guidelines[14] performed on August 07, 2021.

Abbreviations: N_{all} = number of studies among all studies listed in Table S19; N_{pkOA} = number of studies among those studies listed in Table S19 that addressed pkOA.

Cell type	N_{all}	N_{pkOA}	Description
ADRCs	36	35	Adipose-derived regenerative cells
ADSCs	22	18	Adipose-derived stem cells (obtained by culturing ADRCs)
MFF	21	21	Micro-fragmented fat (from liposuction)
CLL	1	1	Centrifuged liposuction liquid
BMA	1	1	Bone marrow aspirate
BMAC	38	26	Bone marrow aspirate concentrate
BM-MSCs	34	25	Bone marrow-derived mesenchymal stem cells
Cs/CPs	2	0	Chondrocytes and chondrocyte precursors
CSCs	1	0	Cartilage stem cells
MACI	1	0	Matrix-induced, autologous chondrocyte implant
S-MSCs	4	1	Matrix-induced MSCs from synovia
Ch-TGFß	2	2	Chondrocytes that overexpress transcription growth factor beta
hUC-MSCs	4	3	Human umbilical cord-derived MSCs
hUCB-MSCs	7	5	Human umbilical cord blood-derived MSCs
P-MSCs	1	1	Placental MSCs
pBSCs	8	4	Activated peripheral blood stem cells
Sum	183	143	

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