Systematic Review

Intra-articular Mesenchymal Stem Cells in Osteoarthritis of the Knee: A Systematic Review of Clinical Outcomes and Evidence of Cartilage Repair

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Purpose: To provide a systematic review of the clinical literature reporting the efficacy of mesenchymal stem cells (MSCs) in terms of clinical outcomes including pain and function and cartilage repair in patients with osteoarthritis. **Methods:** We systematically reviewed any studies investigating clinical outcomes and cartilage repair after the clinical application of cell populations containing MSCs in human subjects with knee osteoarthritis through MEDLINE, EMBASE, the Cochrane Library, CINAHL, Web of Science, and Scopus. Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed. Studies with a level of evidence of IV or V were excluded. Methodological quality was assessed using the Modified Coleman Methodology Score. Clinical outcomes were assessed using clinical scores, and cartilage repair was assessed using magnetic resonance imaging and second-look arthroscopy findings. **Results:** A total of 17 studies that met the criteria of 50 full-text studies were included in this review, with 6 randomized controlled trials, 8 prospective observational studies, and 3 retrospective case-control studies. Among 17 studies, 8 studies used bone marrow—derived MSCs, 6 used adipose tissue—derived stromal vascular fraction, 2 used adipose tissue—derived MSCs, and 1 used umbilical cord blood—derived MSCs. All studies except 2 reported significantly better clinical outcomes in the MSC group or improved clinical outcomes at final follow-up. In terms of cartilage repair, 9 of 11 studies reported improvement of the cartilage state on magnetic resonance imaging, and 6 of 7 studies reported repaired tissue on second-look arthroscopy. The mean Modified Coleman Methodology Score was 55.5 ± 15.5 (range, 28-74). **Conclusions:** Intra-articular MSCs provide improvements in pain and function in knee osteoarthritis at short-term follow-up (<28 months) in many cases. Some efficacy has been shown of MSCs for cartilage repair in osteoarthritis; however, the evidence of efficacy of intra-articular MSCs on both clinical outcomes and cartilage repair remains limited. **Level of Evidence:** Level III; systematic review of level I, II, and III studies.

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Articular cartilage has a limited capacity for spontaneous healing; therefore, any damage from trauma or degeneration ultimately progresses to osteoarthritis.[1] The current treatment approach to osteoarthritic cartilage defects is mainly palliative. A limited number of studies have reported that microfracture has led to improvements in pain and function in patients with osteoarthritis[2,3]; however, microfracture is understood to be most appropriate for small-sized lesions <2 to 4 cm and to deteriorate within a few years.[4,5] Although autologous chondrocyte implantation has been associated with improved structural and functional outcomes in young patients with focal chondral defects at long-term follow-up,[6-8] this technique is less optimal in elderly patients because of senescence or dedifferentiation of the proliferated chondrocytes.[9] Abrasion arthroplasty can be a valid treatment for cartilage lesions, but particularly for young patients with small lesion.[10] Osteochondral autograft transfer

(OAT) offers the advantage of restoring cartilage tissue as well as subchondral bony tissue but is limited to a small lesion and has donor site morbidity[11]; hence, there is no optimal cartilage repair method for patients with osteoarthritis. Mesenchymal stem cells (MSCs) have garnered significant attention in the field of regenerative medicine because of their self-renewal properties, multilineage differentiation potential, and immunomodulatory capacity.[12] In addition, recent studies supported the enhanced healing process of the host through the paracrine action of MSCs.[13-15] In light of successful preclinical studies on cartilage repair using MSCs,[16-18] the clinical application of MSCs for cartilage repair has been increasing. Many human tissues, including bone marrow, adipose tissue, umbilical cord blood, and synovium, are well-known sources of MSCs.[19]

Although some recent studies reported the clinical benefits of intra-articular MSCs in the treatment of osteoarthritis,[20-22] the clinical efficacy of MSCs in cartilage repair or cartilage protection in osteoarthritis has not been established. In addition, there is little consensus as which cell source, type of cell population, or delivery method should be used; therefore, the purpose of this study was to provide a systematic review of the clinical literature reporting the efficacy of MSCs in terms of clinical outcomes including pain and function and cartilage repair in patients with osteoarthritis. We hypothesized that the intra-articular MSCs would enhance clinical outcomes and allow for cartilage repair in patients with knee osteoarthritis.

Methods

Data and Literature Sources

This systematic review was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[23] A literature search was undertaken in MEDLINE, EMBASE, the Cochrane Library, CINAHL, Web of Science, and Scopus. The date was restricted to all published studies until March 31, 2017. The search was conducted on April 30, 2017. The search specifics were: ("mesenchymal stem cell" OR "mesenchymal stromal cell") AND ("restoration of cartilage" OR "reproduce cartilage" OR cartilage) AND (human or clinical) NOT animal. A manual search for additional eligible studies that were not found by the automated search was performed using the reference lists of the included studies and relevant review articles. Identified articles were then assessed individually for inclusion. Abstracts and titles were screened for their relevance; then, the full text of the selected studies was reviewed for inclusion.

Study Selection

Studies presented in the English language that assessed clinical outcomes and/or cartilage repair following the administration of a cell population containing MSCs in human knees with osteoarthritis with a level of evidence (LOE) of I, II, or III were eligible. The title and abstract of each publication were independently screened by 2 authors (C-W.H., Y-B.P.) for eligibility. Subsequently, the same 2 authors individually performed the full-text analysis. Disagreements regarding the inclusion of a given study were resolved by consensus or consultation with the other author (H-J.L.).

Assessment of Literature Quality

LOE assessment of all included studies was performed by 2 authors (Y-B.P., S.H.K.) based on previously published criteria.[24] The methodological quality was also assessed by 2 authors (Y-B.P., S.H.K.) based on the Modified Coleman Methodology Score (MCMS).[25] The MCMS grades cartilage-related studies based on the following 11 criteria: study size, mean follow-up period, number of different surgical procedures, type of study, descriptions of the surgical procedure, descriptions of postoperative rehabilitation, inclusion of magnetic resonance imaging (MRI) outcomes, inclusion of histological outcomes, outcome criteria, procedure for assessing clinical outcomes, and descriptions of the subject selection process. The MCMS ranges from 0 to 100 for the grading of study quality as follows: a score >85 = excellent, between 70 and 84 = good, between 55 and 69 = fair, and <55 = poor.

Assessment of Risk of Bias

Risk of bias was assessed using the Cochrane Collaboration's risk of bias tool by 2 authors (Y-B.P., S.H.K.) independently.[26] The following factors were assessed: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias. According to these items, each of included studies was scored as to be at low, unclear, or high risk of bias. Disagreements were resolved by discussion and assessed by kappa value.

Grading of the Quality of the Evidence

The quality of the evidence was determined using the guidelines of the grading of recommendations, assessment, development and evaluation (GRADE) working group by 2 independent authors (Y-B.P., S.H.K.).[27] The grades of evidence definitions were the following categories: (1) high, defined as further research is unlikely to change confidence in the estimate of effect; (2) moderate, defined as further research is likely to have an important effect on confidence in the estimate of effect and may change the estimate; (3) low, defined as further research is very likely to have an important effect on our confidence in the estimate of effect and is

likely to change the estimate; and (4) very low, defined as any estimate of effect is very uncertain. Disagreements were resolved by discussion and assessed by kappa value.

Data Extraction

Two authors (C-W.H., Y-B.P.) independently recorded data from each study on the study design, number of cases, concomitant treatment, source site, source (autologous or allogeneic), delivery methods, culture expansion, cell type, number of cells, alignment, activity level, postoperative activity protocol, surgical indication, number of surgeons and facilities, Kellgren-Lawrence grade, age, sex (female/male), body mass index, location, lesion size, follow-up, clinical outcomes, and cartilage repair evaluation using a predefined data extraction form. The identity of the cell populations was determined based on a consensus statement about nomenclature by the International Society of Cellular Therapy.[28] Cell populations were classified as bone marrow–derived MSCs (BM-MSCs), adipose-derived mesenchymal stem cells (ASCs), adipose-derived stromal vascular fraction (ADSVF), and umbilical cord blood–derived MCSs (UCB-MSCs).

Results

After the selection process, 17 of 50 studies were included.[20-22,29-42] The selection process for the studies is shown as a flow diagram in Fig 1. The 17 studies included 499 knees with osteoarthritis. The mean age was 57.3 years. The Kellgren-Lawrence grade varied from grade 1 to 4. The mean follow-up period was 20 months (range, 6-84 months). Among these 17 studies, 6 were randomized controlled trials, 8 were prospective observational studies, and 3 were retrospective case-control studies.

LOE and Quality of Evidence

There were 6 studies with LOE I, 8 with LOE II, and 3 with LOE III (Table 1). No studies were deemed excellent, whereas 9 (53.0%) were of poor quality (Table 1). The mean MCMS was 55.5 ± 15.5 (range, 28-74). Further details regarding the LOE and MCMS are shown in Table 2.

Assessment of Risk of Bias

The results of assessment of risk of bias on included studies are summarized in Figure 2. All studies using autologous cells, which needed additional processing to obtain MSCs, were rated as having a high risk of performance or detection bias.[22,29-31,33-42] Moreover, all studies designed as an observational study or case-control study were rated as having a high risk of selection or performance bias because these design studies could not perform randomization.[21,22,29-31,33-36,39,40] The studies by Koh et al.[37] and Wakitani et al.[41] did not clearly report clinical outcomes or report specific scores completely and thus were rated as having an additional high risk of attrition and reporting bias. The studies of Vega et al.,[20] Koh et al.,[37] and Emadedin et al.[31] reported some clinical or image outcomes without specific scores; thus, the reporting bias for this study was rated as high. The number of included cases in the studies of Davatchi et al.,[30] Orozco et al.,[39] Emadedin et al.,[31] and Park et al.[21] was too small and were therefore rated as high in other bias. Moreover, the studies of Bui et al.,[29] Koh et al.,[36,37] Wakitani et al.,[41] Wong et al.,[42] Kim et al.,[34,35] and Park et al.[21] performed additional procedures including platelet-rich plasma (PRP) injection, high tibial osteotomy (HTO) or microfracture and thus were also rated as high in other bias. The interrater agreement according to the kappa value ranged from 0.73 to 0.86, which referred as good to excellent agreement.

GRADE Evidence Quality of Each Outcome

GRADE evidence quality of each outcome is summarized in Appendix Table 1 (available at www.arthroscopyjournal.org). Five outcome categories were evaluated that are frequently used clinically. There were 1 of high quality, 6 of moderate quality,[22,32,33,38,40,42] 5 of low quality,[21,34,35,37,41] and 5 of very low quality[29-31,36,39] regarding final grade of evidence for each study. The final grade of evidence in outcomes of visual analog scale, Western Ontario and McMaster Universities Osteoarthritis Index, Lysholm and Tegner, International Knee Documentation Committee (IKDC), Knee Society Score, and Hospital for Specific Surgery (HSS) scores were low or very low because of the heterogeneity of included studies, however. The quality of study design showed limitations because many prospective observational studies and any other evidence of studies, such as case-control study, were included in this review. The interrater agreement of the final grade of evidence according to the kappa value was found ranged as 0.82 to 0.89, which is considered excellent agreement.

Identity of the Cell Population, Cell Source, and Delivery Method

The study design, identity of the cell population, cell source site, cell source, delivery method, number of cells, alignment, activity level, postoperative activity protocol, surgical indication, and number of surgeons and facilities are summarized in Table 2 and Appendix Table 2. In terms of the cell population identity, 8 studies used BM-MSCs, 2 used ASCs, 6 used ADSVF, and 1 used UCB-MSCs. With regard to cell source, 14 studies used autologous cells, whereas 3 used allogeneic cells. With terms of delivery method, 7 studies delivered cells using 2-stage injection (direct injection of autologous cells after culture expansion), 2 used direct

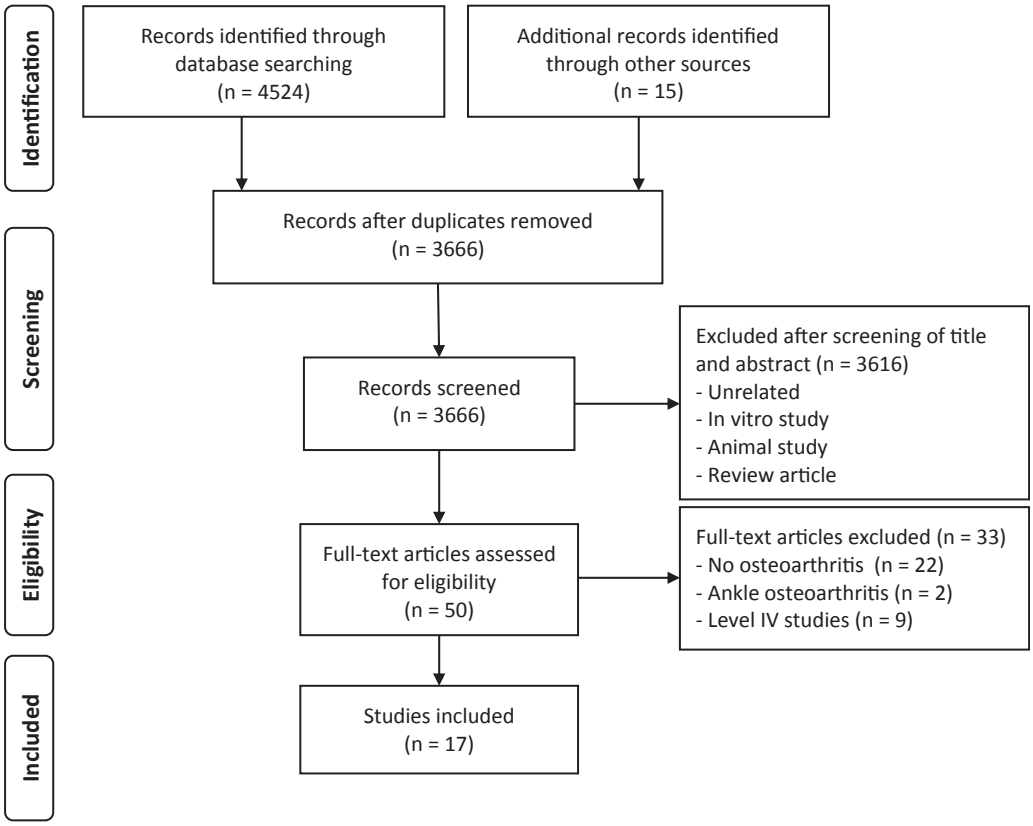

Fig 1. Flow diagram of the selection process for articles.

injection without arthroscopic guidance, 2 used direct injection under arthroscopic guidance (direct injection of autologous cells without culture expansion), 2 used direct injection both with and without arthroscopic guidance (direct injection of autologous cells without culture expansion), 2 used 1-stage injection (direct injection of culture-expanded allogeneic cells), 1 used 2-stage implantation (implantation through an arthrotomy of autologous cells after culture expansion), and 1 used 1-stage implantation (implantation through an arthrotomy of culture-expanded allogeneic cells).

Table 1. The Level and Quality of Evidence of the Clinical Studies

	Study, n (%)
Level of evidence	
I	6 (35.3)
II	8 (47.1)
III	3 (17.6)
Quality of evidence*	
Excellent	0 (0.0)
Good	4 (23.5)
Fair	4 (23.5)
Poor	9 (53.0)

*The quality of evidence was classified according to the Modified Coleman Methodology Score (0-100): >85 = excellent, between 70 and 84 = good, between 55 and 69 = fair, and <55 = poor.

Among 17 studies, 9 involved concomitant treatments including HTO, PRP injection, microfracture, multiple drilling, or hyaluronic acid injection.

Clinical Outcomes

Clinical outcomes are summarized in Table 3. Among 17 studies, 15 reported improvements in clinical outcomes, whereas 2 reported no improvement or no difference. Among 7 studies involving comparison with a control group, 4 studies reported better clinical outcomes in the MSC group,[20,37,38,42] 2 reported no difference,[32,41] and 1 reported no difference at final follow-up, with poor baseline outcomes in the MSC group.[36] All 8 prospective observational studies reported improved clinical outcomes at final follow-up. One study compared the intra-articular injection of autologous ADSVF with PRP to the intra-articular injection of autologous ADSVF under arthroscopy with a fibrin scaffold.[35] Significant improvements were shown in both groups, and there were significant differences in the IKDC scores at final follow-up (55.8 in injection vs 64.8 in arthroscopy, $P = .049$). The authors concluded that injection with fibrin under arthroscopy was a superior method for treating osteoarthritis. In a study that evaluated the effect of a fibrin scaffold on ADSVF therapy for osteoarthritis,[34] IKDC scores and the Tegner

Table 2. Details of Studies on Osteoarthritis Using MSCs

Author(yr)	LOE	MCMS	Study Design	No. of Cases (Study/Control)	Concomitant Treatment	Source Site	Source	Delivery Method	Culture Expansion	Entity of Cells	No. of Cells
Wakitani (2002)	I	54	RCT	24 (12/12)	HTO	BM	Autologous	2-stage implantation	20 d	BM—MSCs	1.3×10^7
Davachi (2011)	II	39	POS	4	None	BM	Autologous	2-stage injection	4-5 wk	BM—MSCs	$0.8\text{-}0.9 \times 10^7$
Emadedin (2012)	II	50	POS	6	None	BM	Autologous	2-stage injection	7 d 2 passages	BM—MSCs	$2\text{-}2.4 \times 10^7$
Wong (2013)	I	73	RCT	56 (28/28)	HTO, microfracture	BM	Autologous	2-stage injection	22 ds Passage	BM—MSCs	1.4×10^7
Orozco (2013)	II	50	POS	12	None	BM	Autologous	2-stage injection	22 d	BM—MSCs	4×10^7
Vega (2015)	I	74	RCT	30 (15/15)	Control: HA	BM	Allogeneic	1-stage injection	22 d	BM—MSCs	4×10^7
Gupta (2016)	I	73	RCT	60 (40/20)	HA injection	BM	Allogeneic	1-stage injection	21 d	BM—MSCs	$2.5\text{-}15 \times 10^7$
Lamo-Espinosa (2016)	I	65	RCT	30 (20/10)	HA	BM	Autologous	2-stage injection	3-4 wk	BM—MSCs	$1, 10 \times 10^7$
Jo (2014)	II	69	POS	18	None	Adipose	Autologous	2-stage injection	21 d	ASCs	$1.0, 5.0, 10.0 \times 10^7$
Pers (2016)	II	69	POS	18	None	Adipose	Autologous	2-stage injection	14 d	ASCs	$0.2, 1, 5 \times 10^7$
Koh (2012)	III	28	Case control	50 (25/25)	PRP	Adipose	Autologous	Direct injection	No	ADSVF	$0.12\text{-}0.23 \times 10^7$
Bui (2014)	II	47	POS	21	PRP	Adipose	Autologous	Direct injection	No	ADSVF	NS
Koh (2014)	I	72	RCT	44 (23/21)	HTO, PRP	Adipose	Autologous	Injection under arthroscopy, direct injection	No	ADSVF	4.83×10^7
Kim (2014)	III	34	Case control	56 (17 fibrin, 39 no fibrin)	None	Adipose	Autologous	Injection under arthroscopy	No	ADSVF	4.2×10^7
Kim (2015)	III	34	Case control	40 (20 injection, 20 surgery)	PRP in injection, fibrin in surgery	Adipose	Autologous	Direct injection, injection under arthroscopy	No	ADSVF	4.0×10^6 (MSCs)
Kim (2016)	II	62	POS	24	None	Adipose	Autologous	Injection under arthroscopy	No	ADSVF	4.9×10^7
Park (2016)	II	50	POS	6	Multiple drilling (5×5 mm)	Umbilical cord blood	Allogeneic	1-stage implantation	6 Passage	UCB-MSCs	$1.15\text{-}2.00 \times 10^7$

ADSVF, adipose-derived stromal vascular fraction; ASCs, adipose-derived mesenchymal stem cells; BM, bone marrow; BM-MSCs, bone marrow–derived mesenchymal stem cells; HA, hyaluronic acid; HTO, high tibial osteotomy; LOE, level of evidence; MCMS, Modified Coleman Methodology Score; NS, not specified; POS, prospective observational study; PRP, platelet-rich plasma; RCT, randomized controlled trial; UCB-MSCs, umbilical cord blood–derived mesenchymal stem cells.

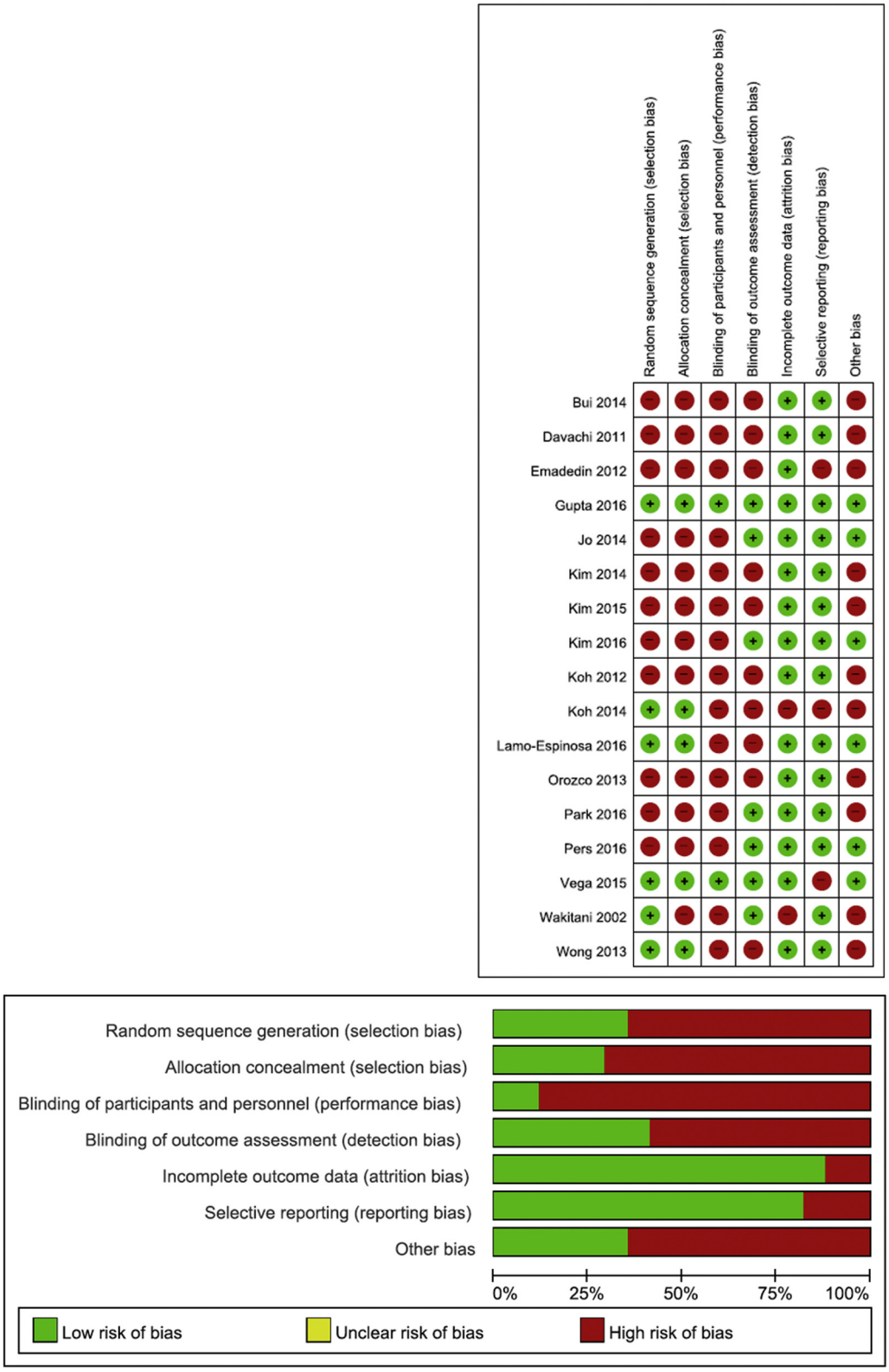

Fig 2. Risk of bias of included studies. Green circle, low risk; red circles, high risk.

activity scale showed significant improvement, but there was no significant difference directly associated with the use of a fibrin scaffold.

Cartilage Repair Evaluation

In terms of cartilage repair, MRI was used in 11 studies and second-look arthroscopy was used in 7 (Table 4).

Table 3. Clinical Outcomes of Studies on Osteoarthritis Using MSCs

Author (yr)	K-L Grade	Age*	Sex (F/M)	No. of Cases (Study/Control)	BMI*	Location	Lesion* (cm^2)	F/U* (mo)	Clinical Outcome	Description
Wakitani (2002)	Alback stages 1 and 2	63	15/9	24 (12/12)	NS	MFC/MTP	NS	16	HSS	81.3 vs 79.2 No significant difference
Davachi (2011)	NS	58	2/2	4	30.3	NS	NS	12	Pain VAS, walking time, number of stairs	Pain, walking time, and number of stairs to climb improved
Emadedin (2012)	4	55	6/0	6	31.6	NS	NS	12	Pain VAS, WOMAC, walking distance	All outcomes improved
Wong (2013)	NS	51	29/27	56 (28/28)	23.9 (median)	Medial comp.	5.0 (median)	24	IKDC, Lysholm, Tegner	All outcomes improved Better scores in the MSC group*
Orozco (2013)	2-4	49	6/6	12	NS	NS	NS	12	VAS, WOMAC, SF-36	All outcomes improved
Vega (2015)	2-4	57	19/11	30 (15/15)	NS	NS	NS	12	VAS, WOMAC, Lequesne, SF-12	All outcomes improved Better improvement in the MSC group*
Gupta (2016)	2-3	56	45/15	60 (40/20)	27.8	NS	NS	12	VAS, ICOAP, WOMAC	No significant differences in all groups
Lamo-Espinosa (2016)	2-4	61	11/19	30 (20/10)	28.4	NS	NS	12	VAS, WOMAC	All outcomes improved Better improvement in the MSC group* Much improvement in the high-dose group
Jo (2014)	3-4	62	15/3	18	26.3	All comp.	4.9	6	VAS, KSS, WOMAC	Significant improvements mostly in the high-dose group
Pers (2016)	3-4	65	10/8	18	27.6	NS	NS	6	VAS, WOMAC, KOOS, SAS, PGA, SF-36	All outcomes improved Significant improvement in the low-dose group only
Koh (2012)	2-4	54	34/16	50 (25/25)	NS	NS	NS	16 (12-18)	VAS, Lysholm, Tegner	All outcomes improved Poorer preoperative scores in the MSC group*
Bui (2014)	2-3	NS	NS	21	NS	NS	NS	8.5	VAS, Lysholm	All outcomes improved
Koh (2014)	<3	53	33/11	44 (23/21)	25.2	NS	NS	24	VAS, Lysholm, KOOS	All outcomes improved Better VAS, KOOS-pain and sport in the MSC group*
Kim (2014)	1-2	57	32/22	56 (17 fibrin, 39 no fibrin)	26.6	NS	5.7	28 (24-34)	IKDC, Tegner	All outcomes improved No difference between groups
Kim (2015)	1-2	59	26/14	40 (20 injection, 20 surgery)	26.8	MFC, LFC, trochlea	5.6	28 (24-42)	IKDC, Tegner	All outcomes improved Better scores in the surgery group*
Kim (2016)	1-2	58	15/9	24	26.6	NS	6.2	28 (24-34)	IKDC, Tegner	All outcomes improved
Park (2016)	NS	59	4/2	6	26.4	MFC/LFC	5.9	84	VAS, IKDC	All outcomes improved

Comp., compartment; F/U, follow-up; HSS, Hospital for Specific Surgery; ICOAP, intermittent and constant osteoarthritis pain; IKDC, International Knee Documentation Committee; K-L, Kellgren-Lawrence; KOOS, Knee Injury and Osteoarthritis Outcome Score; LFC, lateral femoral condyle; MFC, medial femoral condyle; MSC, mesenchymal stem cell; MTP, medial tibial plateau; NS, not specified; PGA, Patient Global Assessment; SAS, Short Arthritis Assessment Scale; SF-12. Short Form-12; SF-36, Short Form-36; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

*Data presented as mean.

Table 4. Evaluation of Cartilage Repair of Studies on Osteoarthritis Using MSCs

Author (yr)		MRI	Description	Second-Look Arthroscopy	Descriptions	Histologic Analysis	Description
Wakitani (2002)		No		42-wk Arthroscopic score	Whitish repair tissue, softer than normal 10.4 vs 8.0*	Wakitani score	Hyaline-like cartilage 5.0 vs 2.7*
Davachi (2011)		No		No		No	
Emadedin (2012)		6 mo	Cartilage thickness increase, extent of tissue repair	No		No	
Wong (2013)		12 mo	MOCART score 62.3 vs 43.2*	No		No	
Orozco (2013)		6, 12 mo	T2 mapping: poor cartilage area decreased (27%), quality improvement (11/12)	No		No	
Vega (2015)		12 mo	T2 mapping: poor cartilage area decreased,* cartilage quality improved in the MSC group*	No		No	
Gupta (2016)		6, 12 mo	WORMS: no significant change in score in all groups	No		No	
Lamo-Espinosa (2016)	RCT	6, 12 mo	WORMS: slight improvement only in high-dose group	No		No	
Jo (2014)		3, 6 mo	Gradual regeneration over time Decreased cartilage defect in the high-dose group*	6 mo	White smooth surface Improved ICRS grade*	ICRSII score	Hyaline-like cartilage, ICRS 21-52*
Pers (2016)		3-4 mo	dGEMRIC, T_{1rho} 3 of 6: possible improvement	3 mo 11 of 18	Severe OA	PS100, CD 34, Ki67 stain	Only 1: stem cell–grafted cartilage
Koh (2012)		No		No		No	
Bui (2014)		6 mo	Partly regenerated cartilage	No		No	
Koh (2014)		No		19.8 mo (14-24)	Better ICRS grade in the MSC group*	No	
Kim (2014)		No		12.3 mo (9-16)	Better ICRS grade with fibrin scaffold*	No	
Kim (2015)		No		12.4 mo (10-15)	Better ICRS grade in the surgery group*	No	
Kim (2016)		24 mo	MOAKS: improvement in size and thickness of cartilage loss,* MOCART: 69.8	No		No	
Park (2016)		3 yr	dGEMRIC Relative delta R1 index: 1.44	12 wk 1 yr	White smooth surface Improved ICRS grade	2 of 6	Hyaline-like cartilage

dGEMRIC, delayed gadolinium-enhanced magnetic resonance imaging of cartilage; ICRS, International Cartilage Repair Society; MOAKS, MRI Osteoarthritis Knee Score; MOCART, Magnetic Resonance Observation of Cartilage Repair Tissue; MSC, mesenchymal stem cell; WORMS, Whole-Organ Magnetic Resonance Imaging Score.

*Indicates statistically significant difference between groups.

Based on MRI evaluation, 9 studies reported improvements in cartilage status, whereas 2 studies reported little or no improvement.[32,40] Among 4 comparative studies that used MRI evaluation, 2 reported significantly high Whole-Organ Magnetic Resonance Imaging Score (WORMS) scores for cartilage quality in the MSC group,[20,42] whereas 1 reported no significant difference in WORMS scores.[32] The other study reported improved WORMS scores for all groups at 6 months, which was deteriorated in the control and low-dose groups but maintained in the high-dose group at 12 months.[37] Among 7 prospective observational studies that used MRI evaluation, 6 reported improvements in cartilage repair, whereas 1 reported improvements on delayed gadolinium-enhanced MRI of cartilage and T_{1rho} in 3 of 6 patients.[40]

On second-look arthroscopy, 6 studies reported improved cartilage status, whereas 1 reported that all patients showed signs of severe osteoarthritis (Osteoarthritis Research Society International histologic grade > 3).[40] In the 2 comparative studies that used second-look arthroscopy, improved arthroscopic scores or International Cartilage Repair Society cartilage grades were observed in the MSC group.[37,41] Histologic analysis was performed in 4 studies. Although 3 studies reported that histology showed hyaline-like cartilage, the remaining study reported that osteoarthritic chondrocytes were observed and that stem cell grafting on the cartilage surface was observed in only 1 of 11 cases.[40]

Discussion

The principle findings of this study showed that intra-articular MSCs for the treatment of knee osteoarthritis had limited evidence for clinical outcomes and cartilage repair. Clinical outcomes such as pain and function were improved after the application of intra-articular MSCs at short-term follow-up in many cases. Several studies reported improved cartilage state after MSCs application; however, in randomized controlled trials, there were controversial results in clinical outcomes and cartilage repair. In addition, concomitant treatments were performed in several studies. Further high-quality studies with long-term follow-up are required to validate the clinical efficacy of MSC therapy in knee osteoarthritis.

This study showed that MSCs were very often associated with favorable clinical outcomes in osteoarthritis in terms of pain and function. Several assessment tools for pain and function were used to evaluate clinical outcomes, which involved patient-reported surveys assessing pain, functional level, activity level, and health status. Fifteen studies reported improvements in clinical outcomes or significantly better clinical outcomes in the MSC group, whereas 2 studies reported no benefit on clinical outcomes.[32,41] One study reported that there was no significant difference in clinical outcomes among all groups.[31] The other study reported that the improvement of the HSS score was higher in the MSC group from baseline to 16-month follow-up (16.3 vs 12.9), although the HSS scores at final follow-up were not significantly different (81.3 in the MSC group vs 79.2 in the control group). In several studies, HTO was performed at the time of surgery, which has been known to be effective in cases of knee osteoarthritis with varus deformity.[43] In addition, a recent review study reported that cartilage repair procedures in conjunction with HTO provided reliable functional improvement at mid- and long-term follow-ups and were associated with the potential for delayed or prevented knee arthroplasty surgery.[44] Some studies included in this review used PRP to enhance cartilage repair[29,35-37]; however, PRP has only shown pain relief and functional improvement in knee osteoarthritis at 1 year postinjection.[45] Overall, the follow-up period of the studies included in this review was short (mean, 20 months; range, 12-84 months). Most studies had follow-up periods <24 months, and only 1 study had a mid-term follow-up of 84 months.[21] Long-term studies without adjuvant treatments are required to evaluate the impact of MSCs in knee osteoarthritis.

The efficacy of MSCs on cartilage repair remains unclear in this review. Among 11 studies, 9 studies reported improved cartilage status on MRI evaluation; however, 3 randomized controlled trials without adjuvant treatment showed different results.[20,32,38] One study reported that improved cartilage quality was observed in the MSC group.[20] Another study reported that the MSC group showed no significant change from baseline to final follow-up and that there was no difference between groups in terms of the WORMS score.[32] The third study reported that, despite improved WORMS scores at 6 months in all groups, the scores were worse than baseline in the control and low-dose groups at 12 months and were maintained only in the high-dose group.[38] The remaining 3 randomized controlled trials showed improved cartilage status in the MSC group on either MRI evaluation at 12 months[42] or second-look arthroscopy at 10 and 20 months.[37,41] In all of those studies, however, HTO was performed at the time of MSC therapy. The efficacy of cartilage repair procedures with concomitant HTO is controversial. Some studies of HTO plus cartilage repair procedures showed good cartilage repair rates of >80%[46] and a higher incidence of a smooth cartilage surface compared with HTO without cartilage repair procedure.[47] Other studies, however, reported that HTO without a combined cartilage repair procedure was associated with the repair of degenerated articular cartilage.[48,49] In addition, a study comparing HTO plus

cartilage repair procedures and HTO alone reported no difference in cartilage repair between the 2 groups[50]; therefore, we believe that well-designed, long-term studies of MSC therapy without adjuvant treatments are necessary to accurately assess the efficacy of MSCs on cartilage repair in knee osteoarthritis. Moreover, further studies also need to determine the durability and quality of the repaired cartilage tissue and the association between the extent of cartilage repair and clinical improvement.

Because the existing clinical studies on MSCs have all used various types of cell populations, delivery methods, and adjuvant treatments, it was difficult to draw conclusions as to the effectiveness of MSCs on clinical outcomes and cartilage repair in knee osteoarthritis. The types of cell populations used in MSC therapy for knee osteoarthritis in the studies included in this review were BM-MSCs, ASCs, ADSVF, and UCB-MSCs. First, the various types of cell populations may lead to different clinical outcomes and degrees of cartilage repair because of variable chondrogenic differentiation potential and immunomodulatory capacity.[51-53] In addition, some studies erroneously used the term ASCs interchangeably with ADSVF, but the latter contains only a small amount of MSCs.[29,33-37] ADSVF is a pellet of cells derived from the centrifugation of lipoaspirates, which are heterogeneous cells containing pericytes, endothelial cells, smooth muscle cells, fibroblasts, and macrophages, along with a small fraction of ASCs.[28,54] Using the correct terminology is extremely critical to prevent confusion in interpreting the results of a given stem cell—based therapy and to correctly assess the scientific rationale for MSC therapy.[55] Regarding delivery methods, both surgical implantation and intra-articular injection have been used for MSC therapy in knee osteoarthritis. Osteoarthritis is a joint disease involving articular cartilage degeneration, synovial hypertrophy, and inflammation; therefore, it appears logical that MSCs be locally administered into the joint. As mentioned previously, several adjuvant treatments including HTO, PRP, hyaluronic acid injection, and arthroscopic debridement were performed in conjunction with MSC therapy, and HTO itself may improve pain, function, and degenerated cartilage status in knee osteoarthritis with varus deformity. Biological treatments such as PRP have gained attention because of their minimal invasiveness and lower cost,[56] and the application of PRP in knee osteoarthritis showed improvements in pain and function over a short period (12 months).[45] Hyaluronic acid is also recommended in knee osteoarthritis for short-term improvements in pain and function outcomes,[57] but, to date, only limited evidence regarding the clinical benefit of MSCs for knee osteoarthritis has been reported. Clearly, many aspects of MSC therapy still require to be optimized and standardized.

Limitations

Several limitations needs to be addressed. First, some outcome assessment tools were used to evaluate clinical outcomes; therefore, it was difficult to assess quantitatively using specific outcome as a primary outcome. Second, different cell populations, cell sources, and delivery methods were used in the included studies. This heterogeneity could induce different clinical outcomes and cartilage repair. Finally, several adjuvant treatments including HTO that could affect clinical outcome and cartilage repair were used in several studies. Because of this, we did not perform a quantitative analysis of the studies reviewed, which limits the conclusions made by this systematic review.

Conclusions

Intra-articular MSCs provide improvements in pain and function in knee osteoarthritis at short-term follow-up in many cases. Some efficacy has been shown of MSCs for cartilage repair in osteoarthritis; however, the evidence of efficacy of intra-articular MSCs on both clinical outcomes and cartilage repair remains limited.

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Appendix Table 1. GRADE Evidence Quality for Each Outcome

	Quality Assessment					Summary of Findings			
						No. of Patients			
No. of Studies	Design	Quality	Consistency	Directness	Other Modifying Factors	Stem Cell	Control	Summary	Quality
VAS scores									
12	RCT: 4 POS: 7 Any other evidence: 1	Serious limitation (−1)	Important Inconsistency (−1)	Direct	Strong evidence of association (+1)	208	91	VAS scores were improved in 11 articles/1 level II study does not show statistical difference	Low
WOMAC scores									
7	RCT: 3 POS: 4	Serious limitations (−1)	Important Inconsistency (−1)	Direct	Strong evidence of association(+1)	129	45	WOMAC scores were improved in 6 articles/1 level II study does not show statistical difference	Low
Lysholm and Tegner scores									
7	RCT: 2 POS: 2 Any other evidence: 3	Very serious limitations (−2)	No important inconsistency	Direct	High risk of reporting bias (−1)/Imprecise data (−1)	211	74	Tegner and Lysholm scores were improved	Very low
IKDC scores									
4	POS: 2 Any other evidence: 2	Very serious limitations (−2)	No important inconsistency	Direct	High risk of reporting bias (−1)/Strong evidence of association(+1)	126	—	IKDC scores were improved	Very low
KSS and HSS scores									
2	RCT: 1 POS: 1	Serious limitations (−1)	Important Inconsistency (−1)	Direct	None	30	12	HSS score: 81.3 vs 79.2 No significant difference KSS score: Significant improvements mostly in the high-dose group	Very low

HSS, Hospital for Specific Surgery; IKDC, International Knee Documentation Committee; KSS, Knee Society Score; POS, prospective observational study; RCT, randomized controlled trial; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Appendix Table 2. Detailed of Included Studies

Author (yr)	Alignment	Activity Level	Postop Activity Protocol	Surgical Indication	No. of Surgeons/ Facilities
Wakitani (2002)	NS	NS	CPM at POD 4 d, PWB at 3-6 wk, FWB at 8 wk	Obliteration of medial compartment	NS/NS
Davachi (2011)	NS	NS	NS	Severe knee OA	NS/1
Emadedin (2012)	NS	NS	NS	Knee OA requiring joint replacement	NS/1
Wong (2013)	No malalignment of femur	Tegner activity scale: 0-2:31, 3-5:24, ≥6:1	NWB for 6 wk, gradual WB, CPM from 3 d to 4 wk	Medial compartment OA	NS/1
Orozco (2013)	NS	NS	NS	K-L 2-4, failure of conservative treatment at least 6 mo	NS/NS
Vega (2015)	NS	NS	NS	K-L 2-4, failure of conservative treatment at least 6 mo	NS/2
Gupta (2016)	NS	NS	NS	K-L 2-3, failure of conservative treatment at least 3 mo	NS/5
Lamo (2016)	Varus or valgus <15°	NS	NS	K-L 2-4, Pain VAS ≥2.5	3/2
Jo (2014)	NS	I:0, II:2, III:12, IV:4*	NWB for 8 wk, FWB at 12 wk	K-L 2-4, pain VAS >4 at least 4 mo	1/1
Pers (2016)	NS	SF-36 physical scale: 32.2	NS	End-stage OA (K-L 3-4), pain at least 12 mo	NS/2
Koh (2012)	Varus or valgus <5°	Tegner activity scale: 1.8	No restrict walking, gradual resumption activities	OA (K-L 1-3)	1/1
Bui (2014)	NS	NS	NS	OA grade 2-3, fail in drug and ACI, Lysholm score <65	NS/1
Koh (2014)	Varus 3.1°	NS	QSE/SLR at POD 1 d, ROM and PWB at 2 wk, FWB at 4 wk	K-L 1-3, failure of conservative treatment	2/1
Kim (2014)	Varus or valgus <5°	Tegner activity scale: 2.4	Immobilize for 2 wk, ROM and PWB at 2 wk, FWB at 4 wk, sports at 3 mo	K-L 1-2, failure of conservative treatment at least 3 mo	NS/1
Kim (2015)	Varus or valgus <5°	Tegner activity scale: 2.5	Immobilize for 2 wk, ROM and PWB at 2 wk, FWB at 4 wk, sports at 3 mo	K-L 1-2, failure of conservative treatment at least 3 mo	1/1
Kim (2016)	Varus or valgus <5°	Tegner activity scale: 2.5	Immobilize for 2 wk, ROM and PWB at 2 wk, FWB at 4 wk, sports at 3 mo	K-L 1-2, failure of conservative treatment at least 3 mo	NS/1
Park (2016)	NS	NS	QSE/SLR immediately after surgery, NWB for 3 mo	K-L 3 with ICRS grade 4 chondral lesion, failure of palliative treatment at least 6 mo	1/1

CPM, continuous passive motion; FWB, full weight bearing; IKDC, International Knee Documentation Committee; K-L, Kellgren-Lawrence; NS, not specified; NWB, non-weight bearing; OA, osteoarthritis; PWB, partial weight bearing; QSE, quadriceps strengthening exercise; ROM, range of motion; SF-36, Short Form-36; SLR, straight leg raising exercise; VAS, visual analog scale.

*Activity level I indicates high competitive sportsman/woman; II, well-trained and frequently sporting; III, sporting sometimes; IV, nonsporting.