Evidence-based Guidelines for the use of Stem Cell Therapy

Orthopedic Conditions Supplement

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CONTENTS

ABBREVIATIONS

AAT	:	Autologous Adipose Tissue
ABMC	:	Autologous Bone Marrow Concentrate
ABR	:	Angioconductive Bioceramic Rod
ACD	:	Advanced Core Decompression
ACI	:	Autologous Chondrocyte Implantation
ACL	:	Anteriorc Cruciate Ligament
ACR	:	American College of Rheumatology
ADL	:	Activities of Daily Living
ADMSCs	:	Adipose tissue-Derived Mesenchymal Stem Cells
ADSCs	:	Adipose Derived Stem Cells
AEs	:	Adverse Events
AMIC	:	Autologous Matrix-Induced Chondrogenesis
ARCO	:	Association Research Circulation Osseous
ASES	:	American Shoulder and Elbow Surgeon
ATLA	:	Adult T-cell Leukemia-Associated Antigen
AVN	:	Avascular Necrosis
BBC	:	Bone marrow Buffy Coat
BMA	:	Bone Marrow Aspiration
BMAC	:	Bone Marrow Aspirate Concentrate
BMI	:	Body Mass Index
BMDSCs	:	Bone Marrow Derived Stem Cells
BMMNC	:	Bone Marrow Mono Nuclear Cell
BMMSC	:	Bone Marrow Mesenchymal Stem Cell
CD	:	Core Decompression
CD	:	Cluster of Differentiation
CFU	:	Colony-Forming Unit
CI	:	Confidence Interval
CPGA	:	Collagen/Polyglycolic Acid
CRP	:	C-Reactive Protein
CT	:	Computed Tomography
EF	:	Ejection Fraction
EtD	:	Evidence to Decision
ESWT	:	Extracorporeal Shock Wave Therapy
FBG	:	Fasting Blood Sugar
FCD	:	Focal Cartilage Defect
FDA	:	Food and Drug Administration
FHC	:	Femoral Head Collapse
G-CSF	:	Granulocyte Colony Stimulating Factor
GDG	:	Guideline Development Group
GDT	:	Guideline Development Tool
GRADE	:	Grading of Recommendations, Assessment
HA	:	Hyaluronic Acid
haMPCs	:	Human adipose-derived mesenchymal progenitor cells
HbA1c	:	hemoglobin A1C
HBM-MSCs	:	Human Bone Marrow derived Mesenchymal Stem Cells
HBV	:	Hepatitis B Virus
HCV	:	Hepatitis C Virus
HHS	:	Harris Hip Score
HIV	:	Human Immunodeficiency Virus
HLA-DR	:	Human Leukocyte Antigen –DRisotype
hMSCs	:	Human Mesenchymal Stem Cells
HSCs	:	Hematopoietic Stem Cells

HTO	:	High Tibial Osteotomy
ICOAP	:	the Intermittent and Constant Osteoarthritis Pain
ICRS	:	International Cartilage Repair Society
IKDC	:	International Knee Documentation Committee
ISCT	:	International Society for Cellular Therapy
KL	:	Kellgren–Lawrence
KOOS	:	Knee Injury and Osteoarthritis Outcome Score
KSFS	:	Knee Society Function Score
KSS	:	Knee Society Score
MCID	:	Minimally Clinical Important Difference
MD	:	Mean Difference
MFAT	:	Microfragmented Adipose Tissue
MKSSF	:	Modified Knee Scoring-Short Form
MNC	:	Mononuclear Cell Concentrate
MOAKS	:	MRI Osteoarthrtis Knee Score
MOCART	:	Magnetic Resonance Observation of Cartilage Repair Tissue
MRI	:	Magnetic Resonance Imaging
MSCs	:	Mesenchymal Stem Cells
MVIC	:	Maximal Voluntary Isometric Contraction
MWS	:	Mayo Wrist Score
NCI-CTCAEs	:	National Cancer Institute-Common Terminology Criteria for Adverse Events
NICE	:	National Institute for Health and Care Excellence
NMR	:	Nuclear Magnetic Resonance
NPRS	:	Numeric Pain Rating Scale
NRS	:	Numeric Rating Scale
NSAIDs	:	Non-Steroidal Anti-Inflammatory Drugs
OA	:	Osteoarthritis
OMERACT	:	Outcome Measures in Rheumatoid Arthritis
OAK	:	Osteoarthritis Knowledge Scale
ON	:	Osteonecrosis
ONFH	:	Osteonecrosis of the Femoral Head
ORBITs	:	Outcome Reporting Bias in Trials
PBMSCs	:	Peripheral Blood Mononuclear Cells
PBSCs	:	Peripheral Blood Stem Cells
PICO	:	Population Intervention Comparator Outcome
PLMSCs	:	Placental Mesenchymal Stem Cells
PRGF	:	Platelet Rich Plasma
PRISMA	:	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PROBE	:	Prospective, Randomized, Open-label, Blind End-point
PROMs	:	Patient Reported Outcome Measures
PRP	:	Platelet Rich Plasma
PRWE	:	Patient Rated Wrist Evaluation questionnaire
QDASH	:	Quick Disabilities of Arm, Shoulder & Hand
QoL	:	Quality of Life
RCT	:	Randomized Control Trial
RoB 2	:	Risk of Bias 2
RoB	:	Risk of Bias
RR	:	Relative Risk
SAEs	:	Severe Adverse Events
SCT	:	Stem Cell Therapy

SD	:	Standard Deviation
SDSC	:	Synovium Derived Stem Cell Therapy
SE	:	Standard Error
SF12	:	Short Form-12
SF-36	:	Short Form-36
SMD	:	Standardized Mean Difference
SNAC	:	Scaphoid Non-union Advanced Collapse
SPR	:	Sports and Physical Recreation
SR/MA	:	Systematic Review/Meta-Analysis
SSEP	:	Somatosensory Evoked Potential
SVF	:	Stromal Vascular Fraction
β-TCP	:	β-Tricalcium Phosphate
THR	:	Total Hip Replacement
TKA	:	Total Knee Arthroplasty
UCMSCs	:	Umbilical Cord-derived Mesenchymal Stem Cells
UTC	:	Ultrasound Tissue Characterization
USG	:	Ultrasound
VAS	:	Visual Analog Scale
VISA-P	:	The Victorian Institute of Sport Assessment Patella
WHO	:	World Health Organization
WOMA	:	Western Ontario and Macmaster Universities Arthritis
WORMS	:	Whole-organ magnetic resonance imaging score
YLD	:	Years Lived with Disability

1. OSTEOARTHRITIS

i. **Key question in PICO format**

ii. **Search strategy**

iii. **PRISMA flow diagram**

iv. **Summary of included studies**

v. **Classification of studies based on level of stem cell manipulation**

vi. **Evidence to decision framework**

vii. **Data extraction**

viii. **Publication bias**

ix. **List of excluded studies**

i. Key Question in PICO format:

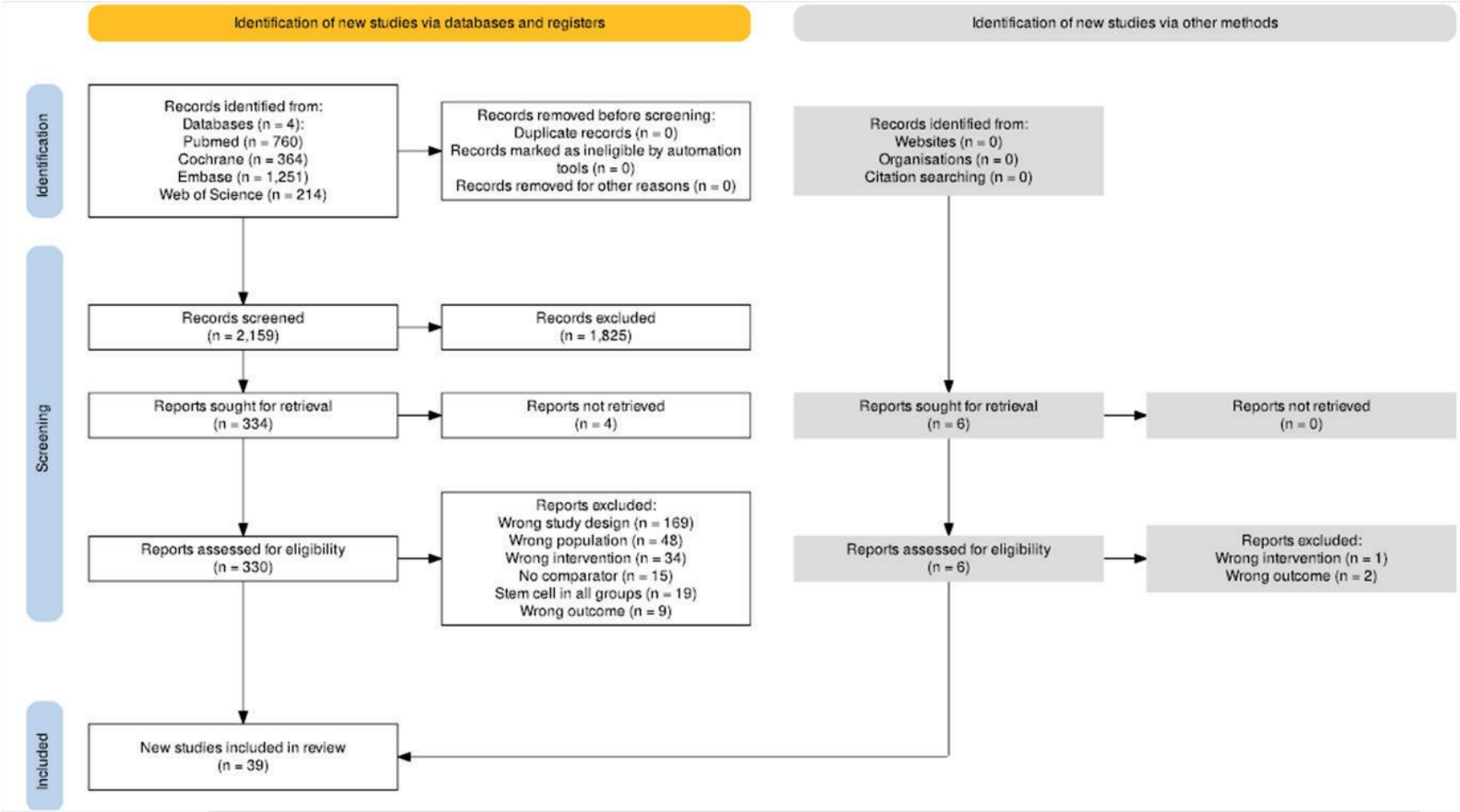
Population: Patients with osteoarthritis
Intervention: Any Stem cell and product derived from stem cells
Comparator: Usual Care/ Conventional Care
Critical Outcomes: Efficacy: Reduction in pain, Disability; Safety: Severe Adverse Events

ii. Search Strategy (September 2023):

Database	No	Search Query
PubMed	#1	(((osteoarthr*[TW]) OR ("osteoarthritis"[MeSH Terms])) OR ((degenerative[TW] AND arthritis[TW]))) OR (arthrosis[TW])
	#2	("Stem Cells"[Mesh] OR "Stem Cell Transplantation"[Mesh] OR "Stromal Cells"[Mesh] OR "stem cell"[tiab] OR "stem cells"[tiab] OR "mesenchymal cell" OR "mesenchymal cells" OR "mononuclear cell" OR "mononuclear cells" OR "progenitor cell" OR "progenitor cells" OR "cord blood cell" OR "cord blood cells" OR "regenerative cell" OR "regenerative cells" OR "stromal cell" OR "stromal cells")
	#3	#1 AND #2 NOT (animals[MH] NOT humans[MH])
Cochrane	#1	(“stem cell” OR “stem cells” OR “mesenchymal cell” OR “mesenchymal cells” OR “mononuclear cell” OR “mononuclear cells” OR “progenitor cell” OR “progenitor cells”):ti,ab,kw OR (“cord blood cell” OR “cord blood cells” OR “regenerative cell” OR “regenerative cells” OR "stromal cell" OR "stromal cells" OR "stem cell transplantation"):ti,ab,kw (Word variations have been searched)
	#2	MeSH descriptor: [Stem Cells] explode all trees
	#3	MeSH descriptor: [Stem Cell Transplantation] explode all trees
	#4	MeSH descriptor: [Stromal Cells] explode all trees
	#5	#1 OR #2 OR #3 OR #4
	#6	MeSH descriptor: [Osteoarthritis] explode all trees
	#7	osteoarthr* OR (degenerative near/2 arthritis) OR arthrosis
	#8	#6 OR #7
	#9	#5 AND #8 [Trials]
Embase	#1	‘stem cell'/exp OR'stem cell transplantation'/exp OR'stroma cell'/exp OR'fetus blood'/exp OR'mesenchyme cell'/exp OR'stem cell':ti,ab,kwOR'stem cells':ti,ab,kwOR'mesenchymal cell':ti,ab,kwOR'mesenchymal cells':ti,ab,kwOR'mononuclear cell':ti,ab,kwOR'mononuclear cells':ti,ab,kwOR'progenitor cell':ti,ab,kwOR'progenitor cells':ti,ab,kwOR'cord blood cell':ti,ab,kwOR'cord blood cells':ti,ab,kwOR'cord blood':ti,ab,kwOR'regenerative cell':ti,ab,kwOR'regenerative cells':ti,ab,kwOR'stromal cell':ti,ab,kwOR'stromal cells':ti,ab,kw
	#2	'osteoarthritis'/exp OR osteoarthritis:ti,ab,kw OR osteoarthr*:ti,ab,kw OR (degenerative:ti,ab,kw AND ('arthritis'/exp OR arthritis:ti,ab,kw)) OR 'arthrosis'/exp OR arthrosis:ti,ab,kw

	#3	('animal'/exp OR'invertebrate'/exp OR 'animal experiment'/de OR 'animal model'/de OR'animal tissue'/de OR'animal cell'/de OR'nonhuman'/de) NOT (('animal'/exp OR'invertebrate'/exp OR 'animal experiment'/de OR'animal model'/de OR'animal tissue'/de OR 'animal cell'/de OR'nonhuman'/de) AND ('human'/de OR'normal human'/de OR'human cell'/de))
	#4	(#1AND#2)NOT#3
Web of science	#1	(((TI=osteoarthr* OR AB=osteoarthr*)) OR (((TI=degenerative OR AB=degenerative) AND (TI=arthritis OR AB=arthritis)))) OR ((TI=arthrosis OR AB=arthrosis))
	#2	((TI="stem cell" OR AB="stem cell") OR (TI="stem cells" OR AB="stem cells") OR (TI="mesenchymal cell" OR AB="mesenchymal cell") OR (TI="mesenchymal cells" OR AB="mesenchymal cells") OR (TI="mononuclear cell" OR AB="mononuclear cell") OR (TI="mononuclear cells" OR AB="mononuclear cells") OR (TI="progenitor cell" OR AB="progenitor cell") OR (TI="progenitor cells" OR AB="progenitor cells") OR (TI="cord blood cell" OR AB="cord blood cell") OR (TI="cord blood cells" OR AB="cord blood cells") OR (TI="regenerative cell" OR AB="regenerative cell") OR (TI="regenerative cells" OR AB="regenerative cells") OR (TI="stromal cell" OR AB="stromal cell") OR (TI="stromal cells" OR AB="stromal cells"))
	#3	#2 AND #1

iii. PRISMA Flow Diagram:



iv. Summary of Included Studies:

Study ID	Population	Intervention	Comparator	Outcome
Vangsness et al. 2014[1] United States	18 to 60 years old candidates for a partial medial Meniscectomy K-L Grade: NA Age: Study: 44.6 ± 9.82, Control: 47.8±8.00	Adult Human Mesenchymal Stem Cells, derived from bone marrow aspirates. A single superolateral knee injection was given within seven to ten days after the partial meniscectomy.	Sodium hyaluronate solution	• Results of MRI defect area of meniscal volume. • Adverse events
Lamo – Espinosa et al. 2020[2] Spain	Males and females aged 18–80, diagnosis of knee OA according to American College of Rheumatology criteria, visual analogue scale (VAS) joint pain ≥2.5, Kellgren-Lawrence radiological classification scale ≥2 Age: median (range) study: 56 (40, 62), control: 54.6 (33,70)	Autologous bone marrow mesenchymal stem cells with platelet-rich plasma Single intra-articular injection of BM-MSCs: 100×10^6, PRGF: 8ml weekly for 3 weeks.	Platelet-rich plasma	• VAS • WOMAC • Adverse events
Goncars et al. 2017[3] Latvia	Degenerative osteoarthritis of knee grade 2/3 K–L classification, at least 6 months of persisting OA symptoms. VAS: NA Age: Study: 53.44+15years, control: 58.55+ 13 years	Bone-marrow-derived mononuclear cells (BM-MNC) Groupsingle intra-articular bone marrow-derived mononuclear cell injection	Three sodium hyaluronate intra-articular injections each one performed a week apart	• KOOS
Lee et al. 2019[4] South Korea	18 and 75 years of age with OA of the knee joint (K-L grade 2 to 4) and had a mean pain intensity of 4 or more on a 10-point VAS for at least 12 weeks. Age - MSC = 62.2±6.5; Control =	Adipose-derived mesenchymal stem cells Three weeks after lipoaspiration, one autologous AD-MSC injection or normal saline injection was administered intra-articularly in the	Normal saline	• MRI defect area • Adverse events

	63.2±4.2	outpatient clinic. Patients were followed up at 1,3, and 6 months after the injection		
Soltani et al. 2018[5] Iran	Patients with knee OA grades 2-4 based on the K-L criteria in knee standing anteroposterior and lateral radiographs. The mean pre intervention VAS values of the MSC and control groups were both 6.90 SVF left knee = 53 ± 10.97; SVF Right knee = 51 ± 5.95	Placental mesenchymal stem cells PLMSCs (10mL; 0.50.6x10^8)	Normal Saline (10ml)	
Chen at al. 2021[6]	Eligible participants included patients aged 40–80 years (inclusive) with K-L grading I–III. VAS for pain Baseline: 55.39 (21.643) Age Study (16M): 67.7±6.84 Study(32M): 68.6±6.45 Study(64M):64.9±4.91 Control: 70.5±8.37	Adipose-derived stem cells (ADSCs) ELIXCYTE® 64× 10^6 cells, 64M; ELIXCYTE® 32× 10^6 cells, 32M; ELIXCYTE® 16× 10^6 cells, 16M)	Hya Joint Plus, synovial fluid supplement 3mL	
Wong et al. 2013[7] Singapore	Medial-compartment OA with genu varum in patients aged younger than 55 years diagnosed either arthroscopically and/or radiologically. K-L grade/ Baseline VAS- NA Age: median (range) Study: 53(36-54), Control: 49(24-54)	MSCs with hyaluronic acid All patients underwent HTO and microfracture. The cell-recipient group received intra-articular injection of cultured MSCs with hyaluronic acid 3 weeks after surgery.	All patients underwent HTO and microfracture. control group only received hyaluronic acid	• IKDC score • Lysholm score • Tegner Score • MOCART

Wakitani et al. 2002[8] Japan	Patients with medial unicompartmental OA who underwent a high tibial osteotomy. K-L grade/ Baseline VAS- NA	Autologous bone marrow mesenchymal cell	Cell free control	• Knee scores
Zhou et al. 2021[9] China	Age between 18 and 75 years old, presence of clearly indicated articular cartilage lesions on MRI and Kellgren-Lawrence grade ≤level 3. Age Study: 52.27 ± 1.17 Control:51.77 ± 7.55	Knee arthroscopic therapy with autologous IPFP (infrapatellar fat pad) cell concentrates 5 mL of the cell concentrates was injected into the corresponding joint cavity	Regular knee arthroscopic therapy	• WOMAC • VAS • MOCART
Hernigou et al. 2018[10] France	Secondary bilateral osteonecrosis (ON) of the knees related to corticosteroids. Age at time of surgery averaged 28 years ranging 18 to 41 years. All these young patients had taken high doses of corticosteroids (>2000 mg) for different medical conditions. K-L grade/VAS: NA Age 28 (18-41)	Mesenchymal stem cells Treatment was performed by percutaneous injection of 40 mL BMC in the subchondral medial and lateral femorotibial compartments of each knee. The bone marrow concentrate was injected slowly through the trocar and the wound closed using a single nylon suture.	Total knee arthroplasty	• Knee Society score • radiological imaging outcomes
Wang et al. 2016[11] China	Based on 2010 Diagnostic criteria for degenerative knee osteoarthritis established by the American Rheumatology Association, was diagnosed with degenerative osteoarthritis, and the clinical stage reached the advanced stage.	Human umbilical cord mesenchymal stem cell Intra-articular injection of 2.5-3.0 mL human umbilical cord MSCs suspension containing (2-3) $\times 10^7$cells was performed once a month for 2 times	HAsodium hyaluronate by intra-articular injection was used once a week for 5 times as a course of treatment	• WOMAC • SF36
Ho et al. 2022[12] China	Aged between 50 and 65 years, affected by primary OA of the knee of K-L grade 2–3 and with a pain level equal to or higher than 5 on a VAS scale of 10 for at	BM-MSC BM-MSC=6ml of 1 x10^6 cells per ml; HA=6ml Intra-articular knee injection	HA	• VAS • WOMAC

	least 2 months.			
Garay-Mendoza et al 2017[13] Mexico	Patients aged over 30 years with knee OA, with unilateral affection, and at least 6 months of progression. OA grades II and III according to the Kellgren and Lawrence radiological classification system. Age Study: 55.67 ± 12.02 Control: 59.32 ± 10.85	Stem cells 10mL concentrate of BM SCs sourced from 75mL BM aspirate (SC count not mentioned)	Acetaminophen Orally 500 mg every 8h for 6 months.	• VAS • WOMAC • SF-36 • KSS • KSFS
Freitag et al. 2019[14]	Radiological diagnosis of osteoarthritis using the American College of Rheumatology criteria. Radiological grading of Grade II–III OA of the knee as determined by a qualified radiologist using the K-Lsystem. VAS Baseline: NA Age: Control :51.5 ± 6.1, Study arm 1: 54.6 ± 6.3 Study arm 2: 54.7 ± 10.2	Autologous MSCs One-injection group: a single intra-articular injection of 100×10^6 ADMSCs	Conservative management only	• WOMAC • NPRS • KOOS
Baria et al. 2022[15]	Age of 25-75 years Body mass index <40kg/m^2, Symptomatic knee OA (primary and posttraumatic) Radiographic evidence of OA in the target knee (K-L grades 1-4). VAS-ADL Baseline PRP: 50.10 ± 21.73 MFAT: 48.97 ± 22.46	Autologous MFAT Single injection of MFAT or PRP	PRP	• VAS • KOOS • ADL • QoL

Kaszynski et al. 2022[16] Poland	Symptomatic knee OA, the age between 45 and 65 years old, Kellgren–Lawrence OA grades from weak to moderate (K-L I–III). Minimum VAS pain score of 4 and the VAS pain score equal or less than 2 in the contralateral knee.	AAT PRP-Three injections, given a half month apart; AAT- One dose of final liposome product.	PRP	• WOMAC • Timed Up and Go Test • Maximal Voluntary Isometric Contraction (MVIC)
Vega et al. 2015[17] Spain	Grade II-IV osteoarthritis, according to the K-L grading scale 2	Allogenic BM-MSC injection given in medial para patellar area.	HA	• VAS • WOMAC • Monitorization of articular cartilage quality.
Kim et al. 2022[18] Korea	Eligible patients were aged 20-80 years and had symptomatic medial compartment knee OA [K-L] grades 2-4. VAS baseline: NA	ADMSC 1×10^{8}MSCs were administrated in 3mL of normal saline.	Medial open-wedge high tibial osteotomy	• MOCART • MOAKS • WOMAC • KOOS • PROMs
Sadri et al. 2023[19] Iran	18 < Age < 65 K-L grading: II or III VAS equal or more than 3	ADMSC Single injection of 100×10^{6} AD-MSCs; 5 ml	Normal Saline	• WOMAC • VAS • KOOS • SF36
Matas et al. 2019[20] Chile	Symptomatic knee OA (defined by daily pain at the affected joint for at least 3 months before inclusion) with grade 1-3 K-L radiographic changes in the targeted knee, without meniscal rupture. VAS (0-100) baseline: HA: 38.7 ± 19.4 UC-MSC 1: 44.8 ± 16.5 UC-MSC2: 39.4 ± 21.4	Umbilical Cord-Derived Mesenchymal Stromal Cells Three groups- Intra-articular knee injections of HA at baseline and 6 months UC-MSCs at baseline and 6 months, or UC-MSCs only at baseline, followed by placebo at 6 months MSC injections contained 20×10^{6} UC-MSCs in 3cc of saline with 5% AB plasma, HA injections contained 3cc of	HA	• Safety • WOMAC • SF36 • OMERACT • Patient global assessment

		Durolane, and placebo injections contained 5% AB plasma in 3cc of saline.		
Lu et al. 2019[21] China	The study included patients of age between 18 and 70 years old with a definite diagnosis of knee OA according to the American College of Rheumatology Clinical classification criteria for knee osteoarthritis. Below grade 4 by K-L criteria. Age, mean: Study-55.03 (9.19), control-59.64 (5.97)	Autologous Adipose derived MPCs-5×10^7haMPCs The haMPC group was injected with 5×10^7haMPCs (around 2.5 ml) at weeks 0 and 3. Sham injection was performed at weeks 1 and 2.	HA In the HA group, intra-articular injection of HA was administrated once a week, four consecutive weeks (week 0, 1, 2, and 3).	• WOMAC • VAS • SF36
Emadedin et al. 2018[22] Iran	Age 18-65, K-L grades 2, 3, 4, OA diagnosed using X-ray, no severe joint involvement for grade 4 OA, Angle of parenthesis feet not >20, WOMAC pain >25. VAS baseline: NA Age: Study: 51.7 ± 9.2 Control: 54.7 ± 5.3	Autologous bone marrow derived MSC. Each patient in the MSC group receive done intra-articular implantation of $40x10^6$ MSCs in 5ml saline supplemented with 2% human serum albumin.	NS	• VAS • WOMAC
Zhang et al. 2022[23] China	Diagnosis met the diagnostic criteria in the American Rheumatism Association Revised Classification Criteria for Knee Osteoarthritis K-L grade 2–3. Baseline VAS: ------ SVF: 4.04 ± 1.46 HA: 3.64 ± 0.98 Age 20–85 years.	Stromal vascular fraction (SVF) SVF= 5 ml, with an average count of 4.84±1.61 cells. The patient was placed in the supine position with the knee straight. Local sterilization was performed. 5 ml of SVF was injected into the joint cavity via a superior lateral approach under sterile technique by percutaneous puncture with a disposable syringe	HA	• VAS • WOMAC • MRI defect area • K-L grade increase

	Study: 53.98 ± 13.69 Control: 55.63 ± 12.18	once a month for a total of three times.		
Zhang et al. 2022[24]	Age 18 and 70 years, with OA K-L grades 2 and 3. Initial pain evaluated at four or greater on a ten-point VAS in the knee joint.	SVF 4 ml of SVF suspension was injected into the region of the cartilage defect.	HA	• K-L grade increase • Volume of cartilage defect and the volume of healthy cartilage • VAS • WOMAC • WORMS • MORCART
Bastos et al. 2020[25]	The inclusion criteria were patients over age 35 with knee OA (based on American College of Rheumatology criteria) and confirmatory radiographs, K–L grade 1–4, Baseline VAS: NA Age Study 30.6±4.5 control-55.9±13.4	MSCs When reaching the desired number of 40×10^6, cells were suspended in 10 mL PBS supplemented with 2% human albumin in the MSC group.	Corticosteroids	• KOOS • Cytokine analysis
Zaffagnini et al. 2022[26] Italy	18 and 75 years with symptomatic knee OA (K-L grade 1-4) VAS Pain at baseline: MF-AT: 6.6 ± 2.0 PRP: 6.2 ± 2.0	MF-AT MF-AT (5mL) was collected in a 10-mL syringe to be injected into the patient. The injection was performed through a classic lateral parapatellar approach using an 18-gauge needle, with the patient in the supine position and the knee in extension.	PRP	• KOOS • VAS

Gupta et al. 2016[27] India	Males or females in the age range 40–70 years (both inclusive) Radiographic evidence of grade 2 to 3 osteoarthritis based on the Kellgren and Lawrence radiographic entry criteria. Baseline VAS: Study 1:60.9 ± 10.7 Study 2: 73.7 ± 15.2 Control 1: 61.0± 23.8 Study 3: 57.4 ± 29.0 Study 4: 46.6 ± 23.6 Control 2: 65.3 ± 23.8 Age Study 1: 58.10 ± 8.23 Study 2: 57.30 ± 9.45 Control 1: 54.90 ± 8.27 Study 3: 55.00 ± 6.72 Study 4: 54.00 ± 6.73 Control: 56.70 ± 5.19	Human bone marrow derived mesenchymal stem cells (HBM-MSCs).	Placebo	• VAS • ICOAP • WOMAC-OA
Gupta et al. 2023[28] India	Male and female patients aged 40-65 Y Body mass index 30 History of primary osteoarthritis of the knee characterized by pain, requiring the intake of analgesics, Radiograph of the knee joint showing evidence of grade 2 to 3 osteoarthritis based on the Kellgren-Lawrence classification. VAS at baseline: BM-MSC: 66.1±13.96 Placebo: 65.0±13.09	BM-MSC Single intra-articular injection of 25 million BMMSCs suspended in 2 mL plus 2 ml HA.	Placebo	• WOMAC • MRI findings using T2 mapping and cartilage volume

Shapiro et al. 2017[29] USA	Long standing bilateral knee pain from mild to moderate bilateral osteoarthritis despite conventional treatments such as activity modification, weight loss, physical therapy, analgesics, nonsteroidal anti-inflammatory drugs, or injection therapy for at least 6 weeks. K-L score less than 4. Baseline VAS: BMAC: 3.1 (0 to 8.1) Placebo: 2.9 (0 to 7.0)	Bone marrow aspirate concentrate with platelet free plasma 15 ml BMAC injected in the randomly assigned knee. Both knees were aspirated before the injection.	Saline: The contralateral knee was injected with 15 mL of sterile saline. Both knees were aspirated before the injection.	• ICOAP • VAS
Lamo-Espinosa et al. 2016[30]	Males and females aged 50–80, diagnosis of knee OA according to American College of Rheumatology criteria, VAS joint pain ≥2.5, K-L radiological classification scale ≥2.	BM-MSC plus HA Intra-articular injection of 10×10^6 autologous cultured BM-MSCs in 1.5ml Ringer's lactate solution OR 100×10^6 autologous cultured BM-MSC in 3ml Ringer's lactate solution followed by an intraarticular injection of 4ml HA.	HA Control group, constituted by patients who received a single intra-articular injection of 60 mg HA (Hyalone®) in a final volume of 4ml	• VAS • WOMAC
Kuah et al. 2018[31] Australia	Males or females aged 40–65 years, Diagnosed K-L grade 1, 2 or 3 knee OA in the study knee. Moderate–severe pain in the study knee, 35–90 mm on a 100 mm visual analogue scale (VAS) Age: Study 1: 55.0 ± 5.15 Study 2: 50.8 ± 7.29 Control: 55.0 ±10.42	MSC	Cell culture media and cryopreservative	• VAS • WOMAC • Quantitative MRI assessments

Dulic et al. 2021[32]	Adult patients with symptomatic knee. OA, K-L grade from 2 to 4 with symptoms for at least 12 months.	BMAC	PRP/HA	• VAS • KOOS • WOMAC • IKDC
Lamo - Espinosa et al. 2018[33]	Males and females aged 50–80, diagnosis of knee OA according to American College of Rheumatology criteria, VAS joint pain ≥2.5, K–L radiological classification scale ≥2.	BM-MSCs plus HA Intra-articular injection of 10×10^6 autologous cultured BM-MSC in 1.5ml Ringer's lactate solution OR 100×10^6 autologous cultured BM-MSC in 3ml Ringer's lactate solution followed by an intraarticular injection of 4ml HA.	HA Control group, constituted by patients who received a single intra-articular injection of 60mg HA (Hyalone®) in a final volume of 4ml	• VAS • WOMAC
Hong et al. 2019[34] China	Age 18–70 years old, Bilateral knees with Grade II-III osteoarthritis, identified by two different observers, according to the K-L grading scale. Bilateral knees with initial pain evaluated at four or greater on a ten-point VAS.	Adipose-derived stromal vascular fraction (AD SVF) single IA injection of SVF 4 ml.	HA Single IA injection of HA 4ml	• WOMAC • WORMS • MOCART
Carvalho Schweich-Adami et al. 2022[35] Brazil	Adult individuals, of both genders, aged between 40 and 75 years, with a diagnosis of OA grade II to IV Kellgren & Lawrence. Significant for PRP, ADSCs+PRP and ADSCs groups. In Control group, the initial score was 6.3 ± 1.15 and in PRP it was 7.6±1.57. ADSCs+PRP it was 8.6±1.1. ADSCs it was 8.9 ±1.10.	Adipose-derived stem cells. The patient received local anesthesia (2% lidocaine) in the lateral interarticular region of the knee. After 10 min, transplantation was performed through an intra-articular injection (21G needle) of ADSCs in the affected knee.	PRP Before transplantation, the patient's knee was submitted to asepsis and then the intra-articular injection of PRP was performed.	• VAS • SF36 • WOMAC • Synovial Fluid analysis

	Age: Control: 41±4.67 PRP: 48±3.51 ADSC+PRP:52.66 ± 4.60 ADSC: 58.5 ± 6.17			
Varma et al. 2010[36]	NA	MSCs	Placebo	• VAS • SRA • QoL
Sadat-Ali et al. 2021[37] Saudi Arabia	Age 45 and 70 years, diagnosed with OAK for at least 12 months based on American College of Rheumatology (ACR) criteria, and unsatisfied with conservative therapy of NSAIDs and physiotherapy Age Study: 56.18±6.56 Control: 56.75±5.77	Autologous Bone Marrow Derived Chondrocytes Cell suspension was injected intra-articularly in the affected joint as a single-dose injection	NSAIDs and physical therapy as needed	• K-L grading • VAS • MKSSSF • QoL
Hernigou et al. 2020[38]	This study included140 adults aged 65 to 90 years who had comparable pain in both knees. K-L Grade 2 to 4 VAS pain score Baseline Cell therapy: 4.43 (0.54) TKA: 3.4 (2 to 6) Age: (mean, range) 75.4 years (65–90)	MSC Treatment was performed by percutaneous injection of 20mL BMC in the subchondral medial femorotibial compartment of each knee, i.e., 10mL in the medial tibial plateau and 10mL in the medial condyle	TKA	• Cartilage volume changes over time
Garza et al. 2020[39]	Men and nonpregnant women between the age of 40 and 75. Grade 2 or 3 K-L OA on radiograph. Baseline VAS: NA Age: Control: 57.1+/9.1 (41-74) Low dose group: 60.5+/-7.9 (48-71) High dose group: 59.5+/-11.7 (41-74)	Mesenchymal Stromal cells The dose-escalated study used a parallel-group design with 3 arms: high-dose treatment group ($3.0x10^7$ SVF cells), low-dose treatment group ($1.5x10^7$) SVF cells), and placebo control group (zero SVF cells).	Placebo	• WOMAC • MRI Review

Table containing adverse events in individual studies in both intervention and control group:

Study ID	Adverse events in intervention group	Adverse events in control group
Vangsness et al. 2014[1]	• General disorders and administration-site conditions • Infections and infestations • Injury and procedural complications • Investigations • Musculoskeletal and connective tissue disorder • Nervous system disorder	• General disorders and administration-site conditions • Infections and infestations • Injury and procedural complications • Investigations • Musculoskeletal and connective tissue disorder • Nervous system disorder
Lamo-Espinosa et al. 2020[2]	• No serious adverse events or complications derived from the procedures or treatments were noted	
Goncars et al. 2017[3]	Not mentioned	Not mentioned
Lee et al. 2019[4]	• Arthralgia • Joint effusion	• Joint effusion
Soltani et al. 2018[5]	• Four patients in the MSC group had increased local pain and mild effusion	No Adverse events reported
Hong et al. 2019[34]	• Pain of the abdomen, • Muscle soreness after strenuous exercise, sustained about one week after liposuction • Pain and swelling in bilateral knee joints	
Chen at al. 2021[6]	• Musculoskeletal and connective tissue disorders • General disorders and administration site conditions • Infections and infestation • Gastrointestinal disorders • Injection site joint pain • Arthralgia • Injection site joint swelling • Joint swelling	• Musculoskeletal and connective tissue disorders • General disorders and administration site conditions • Infections and infestation • Gastrointestinal disorders • Injection site joint pain • Arthralgia • Injection site joint swelling • Joint swelling
Wong et al. 2013[7]	Not mentioned	Not mentioned
Wakitani et al. 2002[8]	Not mentioned	Not mentioned
Zhou et al. 2021[9]	Not Mentioned	Not mentioned
Hernigou et al.	• Increased duration of hospital stay	

2018[10]		
Wang et al. 2016[11]	• Pain at the injection site • Mild swelling • Joint effusion	• Pain at the injection site • Mild swelling.
Ho et al. 2022[12]	No adverse events reported	No adverse events reported
Garay-Mendoza et al. 2017[13]	• Swelling and pain in the knee the day after the SC-IA injection. • Slight pain and stiffness during the first 48h after the injection	No adverse events mentioned
Freitag et al. 2014[14]	• Discomfort and/or swelling post ADMSC therapy • Two participants reported pain and swelling for 4 weeks following ADMSC therapy and due to observed impact on their usual daily activity this was categorized as a severe AE	
Baria et al. 2022[15]	Not mentioned	Not mentioned
Kaszynski et al. 2022[16]	Not mentioned	Not mentioned
Vega et al. 2015[17]	No major adverse outcomes	No major adverse outcomes
Kim et al. 2022[18]	• There were no grades 3, 4, or 5 AEs by the NCI-CTCAE scale and no SAEs	• There were no grades 3, 4, or 5 AEs by the NCI-CTCAE scale and no SAEs
Sadri et al. 2023[19]	• Swelling of injection-site joint • No SAE	
Matas et al. 2019[20]	• No serious AEs, deaths, permanent disability, neoplasia, or septic arthritis cases were registered during the trial. The most common adverse event related to intra-articular injection was acute synovitis	
Lu et al. 2019[21]	• Transient pain • Swelling of injection-site joint	• One SAE occurred in the HA group and the patient endured infection of right knee joint after 2 months of first injection and the patient withdrew from the study
Emadedin et al. 2018[22]	No major adverse events reported	No major adverse events reported
Zhang S et al. 2022[23]	No adverse events reported	No adverse events reported
Zhang Y et al. 2022[24]	No adverse events reported	No adverse events reported
Bastos et al. 2020[25]	Not mentioned	Not mentioned

Zaffagnini et al. 2022[26]	• The MF-AT group presented a total of 10 mild adverse events after the procedure, including mild or moderate knee pain, joint swelling and/or effusion, and injection site pain. • Patient in the MF-AT group reported pain and edema in the treated leg	• Six mild adverse events were reported after the procedure (knee pain, joint swelling and/or effusion, and injection site pain).
Gupta et al. 2016[27]	• Arthralgia • Pain at Injection site • Synovial effusion • hypersensitivity to IMP (joint swelling)	
Gupta et al. 2023[28]	• Ear and labyrinth disorders • Gastrointestinal disorders • General disorders and administration site conditions • Infections and infestations • Injury, poisoning, and procedural complications • Investigation related • Metabolism and nutrition disorders • Musculoskeletal and connective tissue disorders • Nervous system disorders • Respiratory, thoracic, and mediastinal disorders • Skin and subcutaneous tissue disorders • Vascular disorders	• Gastrointestinal disorders • General disorders and administration site conditions • Infections and infestations • Injury, poisoning, and procedural complications • Investigation related • Metabolism and nutrition disorders • Musculoskeletal and connective tissue disorders • Nervous system disorders • Skin and subcutaneous tissue disorders • Vascular disorders
Shapiro et al. 2017[29]	• Effusions • Warmth	• Effusions • Warmth
Lamo-Espinosa et al. 2016[30]	• No serious adverse events or complications derived from the procedures or treatments were noted	
Kuah et al. 2018[31]	• Arthralgia • Prepatellar bursitis	
Dulic et al. 2021[32]	• Slight swelling up to 7 days after intervention	Slight swelling up to 7 days after intervention
Lamo-Espinosa et al. 2018[33]	• No serious adverse events or complications derived from the procedures or treatments were noted during the follow up.	• No serious adverse events or complications derived from the procedures or treatments were noted during the follow up.
Carvalho Schweich-Adami et al. 2022[35]	Not mentioned	Not mentioned
Varma et al. 2010[36]	NA	NA

v. **Classification of studies on the basis of level of manipulation of the stem cell/ Stem cell derived product used (*interpreted by the Secretariat as defined by CDSCO* and the information provided in the trial itself):***

S. No.	Trial Details	Intervention	Level of manipulation	Information extracted from trial
1.	Lamo-Espinosa et al. J. 2016	BM-MSCs 10×10^6 (low dose) or 100×10^6 (high dose)	More	*"BM-MSCs were generated under good manufacturing practice conditions (GMP) with standard operating procedures…The flasks were maintained in culture at 37 °C in 5 % CO2 atmosphere. The growth medium was changed every 3–4 days."*
2.	Lamo-Espinosa et al. J. 2020	Autologous BM-MSCs (100×10^6)	More	*"BM-MSCs were generated under good manufacturing practice conditions (GMP) with standard operating procedures…The flasks were maintained in culture at 37 °C in 5 % CO2 atmosphere. The growth medium was changed every 3–4 days."*
3.	Kaszynski et al. 2022	Adipocyte-derived mesenchymal cells	Less	*"Around 100 mL of the adipose tissue was harvested and processed with the Lipogems device (Lipogems, Milan, Italy). It is a closed, full-immersion, low pressure cylindrical system to produce a uniform product containing concentrated populations of adipocyte-derived mesenchymal stem cells. The final Lipogems product was collected into the new, sterile tubes."*
4.	Zhang et al. 2022	SVF suspension	Less	*"Briefly, lipo aspirates were washed with phosphate-buffered saline, while the mesh filter was applied to remove containing residual blood cells and tissue fragments. Next, an equal volume of digestive enzyme (type I collagenase with the concentration of 5%; Worthington, Lakewood, NJ, USA) was mixed with the washed adipose tissue and placed in a shaking incubator at 37°C for 30 minutes. The resulting mixture was then centrifuged at a rate of 1000 g for 10 minutes, and subsequently, the supernatant (Eppendorf 5810R, Germany) was dis carded. After this, the remnant SVF at the bottom was resus pended in phosphate-buffered saline (PBS) up to a volume of 4.5ml SVF, whereas an automatic cell counter (Countstar IC1000, China) was used to quantify cell quantity and viability."*

5.	Gupta et al. 2016	Allogeneic mesenchymal stromal cells (Stempeucel®)	More	*"Stempeucel® is a bone marrow-derived, ex vivo expanded, pooled, allogeneic human MSC population. The pooled cells were manufactured in an approved Good Manufacturing Practice (GMP) facility from bone marrow-derived MSCs (BMMSCs) of three different healthy volunteers to produce a working cell bank (WCB). The pooled MSCs from the WCB were further expanded to manufacture the investigational medicinal product, Stempeucel®."*
6.	Gupta et al. 2023	Allogeneic mesenchymal stromal cells (Stempeucel®)	More	*"Stempeucel® is a bone marrow-derived, ex vivo expanded, pooled, allogeneic human MSC population. The pooled cells were manufactured in an approved Good Manufacturing Practice (GMP) facility from bone marrow-derived MSCs (BMMSCs) of three different healthy volunteers to produce a working cell bank (WCB). The pooled MSCs from the WCB were further expanded to manufacture the investigational medicinal product, Stempeucel®."*
7.	Sadri et al. 2023	Allogeneic Adipose-derived mesenchymal stromal cells	More	*"Allogeneic AD-MSCs were provided from GMP-certified allogeneic biobank by CellTech Pharmed Co. AD-MSCs were isolated and cultured in IR-FDA-certified clean room facility at CellTech Pharmed Co under PICS/GMP and ISO9001 regulations."*
8.	Matas et al. 2019	Umbilical Cord-Derived Mesenchymal Stromal Cells (MSCs)	More	*"UC-MSCs were cultured in an International Organization for Standardization 9001:2015 certified Good Manufacturing Practice-type Laboratory."*
9.	Vega et al. 2015	Allogeneic Bone Marrow Mesenchymal Stem Cells: Intra-articular injection of $40x10^6$ cells.	More	*"Cells were processed using good manufacturing practice conditions in the IBGM Cell Pro duction Unit….The mononuclear cell fraction was isolated by density gradient centrifugation, resuspended, and cultured in MSC expansion culture medium29in 175-cm^2 tissue culture flasks, with periodic washing to remove nonadherent cells. When cells reached 80% confluence, they were trypsinized and replated, and the process was repeated for 2 more passages."*

10.	Lu 2019	Human adipose-derived mesenchymal progenitor cell (haMPC)	More	*"Re-Join® is a product composed of in vitro expanded autologous MPCs derived from adipose tissue of patients combined with cell suspension solution."*
11.	Zhou 2021	Fat pad cell concentrates containing MSCs	Less	*"During the knee arthroscopic therapy, partial IPFP tissue was acquired using a standard motorized shaver system. Briefly, 200 mL of the mixture containing fat, synovial tissue, and 0.9% saline was collected by a sterilized arthroscopic setup of the fat collection system connected with suction apparatus. After being filtered twice using a 30-mesh filter (pore size of 550 μm) to remove the synovial tissue, the mixture was centrifuged at 300 × g for 5 min. While the liquid supernatant was discarded, 6 mL of 0.9% saline was used to mix the lipoaspirate to make cell the concentrates. In total, 5mL of the cell concentrates was injected into the corresponding joint cavity, and another 1mL was used for identification by flow cytometry and cultured to determine if the cell concentrates were contaminated ."*
12.	Chen 2021	Allogenic Adipose-derived stem cells (ADSCs)	More-allogeneic cultured	*"The stromal vascular fraction (SVF) was isolated by digesting the adipose tissue with type I collagenase, centrifuged, and cultured at 37 °C in a humidified carbon dioxide incubator for primary culture. The adherent and highly proliferated cells termed ADSCs were detached and propagated to the passage 7 and within predefined population doubling level. The ADSCs were then harvested and formulated at a density of 8 × 10^6 cells/mL with cryoprotectant CryoStor® CS10 (BioLife Solutions). Release testing of ELIXCYTE® for micro biological evaluation (including mycoplasma, sterility, and endotoxin tests) was employed to ensure safety. The product characteristics such as identity (including MSC markers, viable cell count, and cell viability), and tri-line age differentiation properties were also assessed."*
13.	Ho 2022	BM-MSCs	More	*"BM-MSCs at passage 5 were used for intra-articular injection."*
14.	Goncars 2017	Bone-marrow-derived mononuclear cells (BM-MNC)	less	*The bone marrow aspirate was shipped at room temperature to the central cell-processing laboratory and diluted and filtrated and BM-MNCs were isolated and enriched by density gradient with the use of Ficoll–Paque. Premium. The Stem CXP program was used for MNC, CD34+ cell count and cell viability detection".*

15.	Bastos 2019	Bone-derived mesenchymal stem cells (MSCs)- Intra-articular injections	More	*"Cultures were maintained for no more than two passages. The cells met the criteria for mesenchymal stromal cells (MSC) based on colony-forming unit-fibroblast (CFU-F) assay and flow cytometry."*
16.	Freitag 2019	Autologous MSCs	More	*"In summary, lipoaspirate was separated into stromal vascular fraction using enzymatic digestion and centrifugation and later cell culturing performed under hypoxic conditions within standard growth media containing 10% fetal bovine serum (FBS). Cells were cultured until 80% confluency was reached and further cultured until passage 2 (P2). At completion of P2, cells were washed three times to remove FBS and cryopreserved using a validated control rate freezing method."*
17.	Zaffagnini 2022	MFAT	Less	*"The harvested fat was immediately processed using the Lipogems system (Lipogems International Spa, Milan, Italy)"*
18.	Garza 2020	Mesenchymal Stromal cells	Less	*"All tissue processing was done under sterile conditions, within the single sterile GID SVF-2 device, at the point-of-care."*
19.	Emadedin 2018	Autologous bone marrow derived MSC.	More	*"MSCs were isolated, cultured and characterized."*
20.	Lamo-Espinosa et al. J. 2018	BM-MSCs	More	*"BM-MSCs were generated under good manufacturing practice conditions (GMP) with standard operating procedures…The flasks were maintained in culture at 37 °C in 5 % CO2 atmosphere. The growth medium was changed every 3–4 days."*
21.	Shapiro 2016	Bone marrow aspirate concentrate (BMAC)	Less	*"Fifty-two milliliters of bone marrow was aspirated from the iliac crests and concentrated in an automated centrifuge. The resulting BMAC was combined with platelet-poor plasma for an injection into the arthritic knee and was compared with a saline injection into the contralateral knee, thereby utilizing each patient as his or her own control."*
22.	Wong 2013	MSCs	More	*"Autologous MSCs were cultured from bone marrow in a class B clean room environment."*
23.	Kim 2022	ADMSCs	More	*"ADMSCs were isolated from abdominal subcutaneous fat by lipoaspiration and cultured under Good Manufacturing Practices conditions."*
24.	Lee 2019	Adipose-derived mesenchymal stem cells	More	*"AD-MSCs (Jointstem; R-Bio, Seoul, Korea) used in the current study were isolated and cultured."*

* as defined by CDSCO in Annexure- I of the guideline document

vi. Evidence to Decision Framework:

QUESTION

What is the safety and efficacy of Stem Cell Therapy vs usual care in patients with Knee Osteoarthritis?	
POPULATION:	Osteoarthritis
INTERVENTION:	Any Stem cell and product derived from stem cells
COMPARISON:	Usual care/ Standard of Care
MAIN OUTCOMES:	Visual Analogue Scale, WOMAC scores, KOOS scores at 6 months and 12 months
SETTING:	Tertiary care center/Hospital
PERSPECTIVE:	Health Systems
BACKGROUND:	Osteoarthritis, a prevalent degenerative joint disease, poses a substantial global health burden. Mesenchymal Stem Cells (MSCs), known for their regenerative capabilities, have shown promise in preclinical studies for alleviating osteoarthritic symptoms and promoting cartilage repair.
CONFLICT OF INTERESTS:	None

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○No ○Probably no ○Probably yes	Osteoarthritis (OA) is one of the most common causes of pain and disability, representing a significant burden for the individual and for society. The knee is one of the most prevalent among all joint sites affected by OA.	

● Yes ○ Varies ○ Don't know		
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	**VAS at 12 months:** Nine trials with 474 participants reported post score of VAS at the end of 12 months. The mean difference was -1.76 (95% CI: -2.59 to -0.93) between the stem cell and the usual care arm. The difference was statistically significant but less than the MCID of 2, hence unimportant clinically. Three trials with 142 participants reported the absolute change in VAS score at the end of 12 months. The mean difference was -0.39 (95% CI: -1.70 to 0.92) between the stem cell and the usual care arm. The difference was statistically non-significant. **WOMAC at 12 months:** Nine trials with 417 participants reported post score of WOMAC at the end of 12 months. The mean difference was -8.74 (95% CI -16.03 to-1.45) between the stem cell and the usual care arm. The difference was statistically significant but less than the MCID of 20, hence unimportant clinically. Two trials with 166 participants reported WOMAC on a scale of 0-2400 at the end of 12 months. They reported a mean difference of -575.40 (95% CI: -708.26 to - 442.53) between the stem cell arm as compared to the usual care arm. The difference was statistically significant and clinically important. Two trials with 42 participants reported the change in WOMAC score at the end of 12 months. The mean difference was -11.96 (95% CI -22.65 to -1.28) between the stem cell and the usual care arm. The difference was statistically significant but less than the MCID of 20, hence unimportant clinically. **KOOS pain at 12 months:** Four trials with 144 participants reported post score of KOOS pain at the end of 12 months. The mean difference was 23.14 (95% CI: 5.71	The GDG decided an MCID of 20% for VAS, KOOS and WOMAC scores.

	to 40.56) between the stem cell and the usual care arm. The difference was statistically significant and crosses the MCID of 20, hence important clinically. One trial with 98 participants reported the change in KOOS pain score at the end of 12 months. The mean difference was -1.20 (95% CI: -8.16 to 5.76) between the stem cell and the usual care arm. The difference was statistically non-significant. **KOOS Symptom at 12 months:** Three trials with 88 participants reported post score of KOOS symptom at the end of 12 months. The mean difference was 28.07 (95% CI: 7.40 to 48.73) between the stem cell and the usual care arm. The difference is statistically significant and more than the MCID of 20, hence important clinically. One trial with 98 participants reported the change in KOOS symptom score at the end of 12 months. The mean difference was -0.20 (95% CI: - 6.87 to 6.47) between the stem cell and the usual care arm. The difference was statistically non-significant. **KOOS QoL at 12 months:** Three trials with 88 participants reported post score of KOOS QoL at the end of 12 months. The mean difference was 27.64 (95% CI: 8.45 to 46.84) between the stem cell and the usual care arm. The difference was statistically significant and crosses the MCID of 20, hence important clinically. One trial with 98 participants reported the change in KOOS QoL score at the end of 12 months. The mean difference was -1.20 (95% CI: -9.72 to 7.32) between the stem cell and the usual care arm. The difference was statistically non-significant. **KOOS ADL at 12 months:** Three trials with 88 participants reported post score of KOOS ADL at the end of 12 months. The mean difference was 22.67 (95% CI: -1.27 to 46.61) between the stem cell and the usual care arm. The difference was statistically not significant. One trial with 98 participants reported the change in KOOS ADL score at the end of 12 months. The mean difference was -5.30 (95% CI: -13.48 to 2.88) between the stem cell and the usual care arm. The difference was statistically non-significant.	

	KOOS SPR at 12 months: Three trials with 88 participants reported post score of KOOS SPR at the end of 12 months. The mean difference was 18.89 (95% CI: 2.77 to 35.01) between the stem cell and the usual care arm. The difference was statistically significant but less than the MCID of 20, hence unimportant clinically. One trial with 98 participants reported the change in KOOS SPR score at the end of 12 months. The mean difference was -2.70 (95% CI: -13.41 to 8.01) between the stem cell and the usual care arm. The difference was statistically non-significant.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ● Varies ○ Don't know	**Serious Adverse Events:** Twenty-four studies with 1166 participants reported SAEs but did not find any statistically significant difference of SAEs in the stem cell group as compared to the usual care group. Pooled analysis revealed a risk ratio of 0.68 (95% CI: 0.26 to 1.77).	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The evidence in this review is of low to very low quality due to risk of bias, inconsistency and imprecision in the effect shown by stem cell therapy.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	Main outcome is clinical improvement in the form of reduced pain and increased functional activity which is likely to be highly valued by most persons.[40]	
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	It is less clear if benefits of stem cell intervention outweigh the harms, based on limited evidence.	
Resources required		

How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No direct evidence of the resources required in stem cell transplantation in patients with osteoarthritis was identified. According to the websites of Insurance Agencies and third-party agencies, the average cost of SCT for osteoarthritis in India is usually between 3 lakhs to 6 lakhs.[41, 42]	
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ● Moderate ○ High ○ No included studies	No direct evidence was identified.	The GDG members were fairly certain that stem cell therapy requires large resources.
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○Favors the comparison ●Probably favors the comparison ○Does not favor either the intervention or the comparison ○Probably favors the intervention ○Favors the intervention ○Varies ○No included studies	No direct research evidence was identified.	The intervention was not found to be effective and hence the committee deferred to comment on cost effectiveness.
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○Reduced ●Probably reduced ○Probably no impact ○Probably increased ○Increased ○Varies ○Don't know	No research evidence was identified.	As stem cell therapy is an expensive treatment offered only at tertiary care centers, it is likely to increase inequity as it would not be affordable by all.
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○No ○Probably no	Despite uncertainty regarding the medical risks and benefits associated with stem cell injections, patients with orthopedic disorders/disabilities have very high	

● Probably yes ○ Yes ○ Varies ○ Don't know	expectations from stem cell therapy.[43]	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	Feasible to implement in tertiary centres.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Trivial	Small	Moderate	Large		**Varies**	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or	Possibly important	**Probably no important**	No important uncertainty or			

	JUDGEMENT						
	variability	uncertainty or variability	**uncertainty or variability**	variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	**Moderate**	High			No included studies
COST EFFECTIVENESS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Use only in the context of rigorously conducted RCTs	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	●	○	○	○

CONCLUSIONS

Recommendation

Stem cell therapy is **not recommended** in routine practice for the treatment of osteoarthritis. It may be used only in the context of rigorously conducted randomized controlled trials.

Justification

This recommendation has been made as there is very low certainty evidence of trivial reduction in pain and trivial improvement in function. The undesirable effects are variable and heterogenous. In addition, the follow up period is limited to comment on the long-term safety of stem cell therapy. Results should be interpreted with caution, in view of various study limitations like small number of participants and/or events, risk of bias, use of active co-intervention along with stem cell therapy, different sources and varying dose of stem cell used.

vii. Data Extraction

Data Extraction Methods:

Two review authors independently screened the articles retrieved from the searches using the Rayyan online screening tool and determined eligibility by reading the abstract of each study identified by the search. Independent review authors eliminated studies that clearly did not satisfy inclusion criteria and obtained full copies of the remaining studies. The selected studies were read independently by two review authors to identify relevant studies, and in the event of disagreement, a third author adjudicated. The studies were not anonymized in any way before assessment. A PRISMA flow chart was included in the full review, illustrating the status of identified studies. Studies were included in the review irrespective of whether measured outcome data were reported in a 'usable' way.

Both reviewers independently extracted data using a standard form and checked for agreement before entry into Review Manager. Information about all the primary outcomes was included. Multiple reports of the same study were collated, ensuring that each study, rather than each report, was the unit of interest in the review. Characteristics of the included studies were collected in sufficient detail to populate a table of 'Characteristics of included studies' in the full review. The reviewers independently assessed the risk of bias for each study, employing the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions, with any disagreements resolved through discussion. A 'Risk of bias' table was completed for each included study using the 'Risk of bias 2' (RoB 2) tool.

A fixed-effect model or random-effects model was used to estimate the overall direction, size, and consistency of an effect. For dichotomous variables, we computed treatment effects as risk ratios (RR) with 95% confidence intervals (CI). For continuous data, we

employed mean differences (MD) with 95% CI when the results were measured in the same way across different studies. Standardized mean differences (SMD) were used when the results obtained were conceptually the same but measured on different scales. The mean and standard deviations was recorded. In cases, where there was insufficient information available to directly retrieve mean and standard deviations for the changes, they were imputed using methodologies based upon type of available data: interquartile range, complete range, or five-number summary. These calculations are done using this website as mentioned. If the required data were not available, we relied on a comparison of final measurements. We evaluated the direction and size of the effect, also considering the consistency across the selected studies. Clinically meaningful change was considered, taking into account the change in haemoglobin.

In parallel-group RCTs, the individual participant was considered as the unit of analysis. When cross-over trials were incorporated into the meta-analysis, the approach suggested by Elbourne (Elbourne et al. 2002) was followed. These trials were integrated by extracting measurements from experimental intervention periods and control intervention periods and analyzing them as if the trial were a parallel- group trial of intervention versus control. In cases where carry-over was deemed problematic, only data from the first period were included. The effect estimate of cross-over trials was incorporated into a meta-analysis using the generic inverse-variance method.

Dealing with missing data

When published data were missing, incomplete, or inconsistent with RCT protocols, further information has been asked from the authors/manufacturers. The authors were contacted by email in cases where outcome measures of interest were not reported in studies and also studies had not described the randomization or intention-to-treat analysis, or had missing data.

Assessment of heterogeneity

Clinical heterogeneity has been assessed using the Chi^2 test (P value < 0.1 for statistical significance) and I^2 statistic has been employed to quantify heterogeneity. Considerable heterogeneity was considered for percentage of I^2 more than 75%, substantial for percentage between 50% and 90%, moderate if it was between 30% and 60%, and mild if less than 40%. In the presence of statistical heterogeneity (I^2 greater than or equal to 50%), it was reported and possible causes through prespecified subgroup analysis were explored. A random-effects model was applied.

Subgroup analysis

Subgroup analysis was planned for the type of stem cell therapy, source of stem cell, and comparator (active or placebo) provided adequate data was available.

Assessment of reporting biases

For 10 or more included studies, a funnel plot test was conducted for asymmetry to assess any evidence of reporting bias. Additionally, possible sources of asymmetry in a funnel plot were explored.

Data synthesis

A meta-analysis has been undertaken only when participants, interventions, comparisons, and outcomes were judged to be sufficiently similar to ensure an answer that was clinically meaningful and relevant. For the analysis, RevMan 5.4 software was used, the Cochrane Collaboration has been provided by the statistical package or R v4.3.023 with meta v6.5.024, metaphor v4.2.025, metasens v1.5.226, and brms v2.20.127 packages.

GRADE Analysis

As per the recommendations outlined in 'The Cochrane Handbook', chapter 4.6.6., and the 'GRADE handbook for grading quality of evidence and strength of recommendations', a 'Summary of findings' table was included. Using the GRADEpro GDT system, two review authors assessed the overall quality of evidence for each outcome and presented the findings in the SoF tables. Decisions to downgrade the quality of the studies were substantiated through footnotes.

Data Extraction Sheet:

Study ID	Vangsness et al. 2014[1]	Lamo – Espinosa et al. 2020[2]	Goncars et al. 2017[3]	Lee et al. 2019[4]
Study design	Randomized, Double-Blind, Controlled Study (3 arm)	Phase II randomized controlled clinical trial (2 arm)	Randomized control trial (2 arm)	Prospective double-blinded, randomized controlled, phase IIb clinical trial (2 arm)
Place of Study	United States	Spain	Latvia	South Korea
Details of participants	Candidates of age 18 to 60 years old for a partial medial Meniscectomy K-L Grade: NA Age: Study:44.6±9.82, Control: 47.8±8.00	Males and females aged 18–80, diagnosis of knee OA according to American College of Rheumatology criteria, visual analogue scale (VAS) joint pain ≥2.5, Kellgren-Lawrence radiological classification scale ≥2, Age: median (range) study:56 (40,62), control:	Degenerative osteoarthritis of knee grade 2/3 Kallgren–Lawrence classification, at least 6 months of persisting OA symptoms. VAS: NA Age: Study: 53.44 + 15years, Control: 58.55 + 13 years	Age 18 and 75 years of with OA of the knee joint (K-L grade 2 to 4) and had a mean pain intensity of 4 or more on a 10-point VAS for at least 12 weeks. Age– MSC=62.2±6.5; Control= 63.2±4.2

		54.6 (33,70)		
Exclusion criteria	Confirmed ACL or other support-structure damage during partial medial meniscectomy, Grade 3 or 4 articular cartilage damage in the medial compartment of the operative joint, etc	Previous diagnosis of polyarticular disease Severe mechanical deformation Systemic autoimmune rheumatic disease arthroscopy or intraarticular infiltration in the last 6 months Chronic treatment with immunosuppressive or anticoagulant drugs	Age over 75 years, Severe effusion, contracture, and axial deformities in the knee joint, septic arthritis or skin disorders, previous injection in the target knee within two months before and during observation period uses of corticosteroids and immunosuppressive agents	Pregnant women or lactating mothers Patients who received any drug by intra-articular injection for treatment within 2 months prior to this enrolment Patients with Body Mass Index (BMI) > 30.
Details of intervention	Adult Human Mesenchymal Stem Cells, derived from bone marrow aspirates A single superolateral knee injection was given within seven to ten days after the partial meniscectomy	Autologous bone marrow mesenchymal stem cells with platelet-rich plasma single intra-articular injection of BM-MSCs:100×10^6, PRGF: 8ml weekly for 3 weeks	Bone marrow-derived mononuclear cells (BM-MNC) Group single intra-articular bone marrow-derived mononuclear cell injection	Adipose-derived mesenchymal stem cells Three weeks after lipoaspiration, one autologous AD-MSC injection or normal saline injection was administered intra-articularly in the outpatient clinic. Patients were followed up at 1, 3, and 6 months after the injection
Details of comparator	Sodium hyaluronate solution	Platelet-rich plasma	Three sodium hyaluronate intra-articular injections each one performed a week apart	Normal saline
Details of outcome	Results of MRI defect area of meniscal volume	• VAS • WOMAC	• KOOS	• MRI defect area • Adverse events

	Adverse events	• Adverse events		
Notes	Funding - Osiris Therapeutics, Columbia, Maryland	Grants from ISCIII RETIC Program TerCel supported in part by FEDER Funds and the Spanish Ministry of Health.	Funding – not mentioned	Funding: R- Bio Co. Ltd.
Study ID	Soltani et al 2018[5]	Chen at al 2021[6]	Wong et al 2013[7]	Wakitani et al. 2002[8]
Study design	Randomized, double blind, assessor blind, placebo-controlled clinical trial (2arm)	Randomized, active-control, single-blind, multiple-centre clinical trial (4 arm)	Prospective, Randomized Controlled clinical trial	-
Place of Study	Iran	-	Singapore	Japan
Details of participants	Patients with knee OA grades 2-4 based on the K-L criteria in knee standing anteroposterior and lateral radiographs. The mean pre intervention VAS values of the MSC and control groups were both 6.90 SVF left knee= 53 ± 10.97; SVF Right knee= 51 ± 5.95	Eligible participants included patients aged 40–80years (inclusive) with Kellgren–Lawrence (K-L) grading I–III. VAS for pain Baseline: 55.39 (21.643) Age: Study (16M): 67.7±6.84 Study(32M): 68.6±6.45 Study(64M):64.9±4.91 Control: 70.5±8.37	Medial-compartment OA with genu varum in patients aged younger than 55 years diagnosed either arthroscopically and/or radiologically. K-L grade/ Baseline VAS- NA Age: median (range) Study: 53(36-54) , Control: 49(24-54)	Patients with medial unicompartmental OA who underwent a high tibial osteotomy. K-L grade/ Baseline VAS- NA
Exclusion criteria	• Visible knee deformity (varus>10; valgus >20) • Any sort of neoplasia, BMI >35. • Conditions along with impaired immune system • Any inflammation in the joints or secondary OA,	• Surgery history on the target knee joint • Previous intra-articular intervention on the target knee joint within past 3 months • Hypersensitivity to any component used in the	• Joint line congruity angle more than 2 degree • Mal alignment of the knee from femoral causes, • Bicompartmental and tri-compartmental osteoarthritis.	Not mentioned

	Intra-articular injections during the last 3 mo. • History of knee surgery,	study. • Patients already participated in any other interventional study within 4 weeks of entering the study were also excluded	• Patients who were unable to tolerate magnetic resonance imaging (MRI) scans, unable to answer subjective questionnaires, or not mentally fit to provide informed consent were also excluded.	
Details of intervention	Placental mesenchymal stem cells PLMSCs (10 mL; 0.50.6x10^8)	Adipose-derived stem cells (ADSCs) ELIXCYTE® 64×10^6 cells, 64M; ELIXCYTE® 32×10^6 cells, 32 M; ELIXCYTE® 16×10^6 cells, 16 M)	• MSCs with hyaluronic acid • All patients underwent HTO and microfracture. The cell-recipient group received intra-articular injection of cultured MSCs with hyaluronic acid 3 weeks after surgery.	Autologous bone marrow mesenchymal Cell
Details of comparator	Normal Saline (10ml)	Hya Joint Plus, synovial fluid supplement 3 mL	• All patients underwent HTO and microfracture. • Control group only received hyaluronic acid.	Cell free control
Details of outcome	-	-	• IKDC score • Lysholm score • Tegner Score • MOCART	Knee scores
Notes	Funding: National Institute for Medical Research	Funding: Unico Cell BioMed Co. Ltd. and the A+ Industrial	Funding: not mentioned	-

	Development, Iran	Innovative R&D Program, Ministry of Economic Affairs, Republic of China		
Study ID	Hernigou et al. 2018[10]	Wang et al. 2016[11]	Ho et al. 2022[12]	Garay-Mendoza et al. 2017[13]
Study design	RCT	Open-label RCT	Single-centre, single-blind randomized study 2015 to 2020	Open-label phase I/II RCT
Place of Study	France	China	China	Mexico
Details of participants	• Secondary bilateral osteonecrosis (ON) of the knees related to corticosteroids. Age at time of surgery averaged 28 years ranging 18 to 41 years. All these young patients had taken high doses of corticosteroids (> 2000 mg) for different medical conditions. K-L grade/VAS: NA Age 28 (18-41)	• Based on 2010 Diagnostic criteria for degenerative knee osteoarthritis established by the American Rheumatology Association, was diagnosed with degenerative osteoarthritis, and the clinical stage reached the advanced stage.	• Candidates aged between 50 and 65 years, affected by primary OA of the knee of K-L grade 2–3 and with a pain level equal to or higher than 5 on a VAS scale of 10 for at least 2 months.	• Patients aged over 30 years with knee OA, with unilateral affection, and at least 6 months of progression. OA grades II and III according to the Kellgren and Lawrence radiological classification system. Age: Study: 55.67 ± 12.02 Control: 59.32 ± 10.85
Exclusion criteria	Not mentioned	• Rheumatoid and rheumatoid arthritis • Joint tuberculosis/ tumors • Gouty arthritis • Pregnant and lactating female patients	• Hypersensitivity towards HA • On-going or recent steroid-based systemic therapy • Significant hematologic disease • Mechanical knee	• Patients with systemic arthritis, a knee infection or surgery in the last 6 months • An intra-articular injection in the past 3 months • Neurodegenerative,

			instability, ligamentous laxity or deficiency or gross knee deformity • Prior knee surgery.	autoimmune, malignant or traumatic lesions (joint fracture, meniscal or ligament injury)
Details of intervention	Mesenchymal stem cells Treatment was performed by percutaneous injection of 40 mL BMC in the subchondral medial and lateral femorotibial compartments of each knee. The bone marrow concentrate was injected slowly through the trocar and the wound closed using a single nylon suture	Human umbilical cord mesenchymal stem cell Intra-articular injection of 2.5-3.0 mL human umbilical cord MSCs suspension containing (2-3) $\times 10^7$ cells was performed once a month for 2 times	BM-MSC BM-MSC = 6ml of $1x10^6$ cells per ml; HA=6 ml Intra-articular knee injection	Stem cells 10 mL concentrate of BMSCs sourced from 75 mL BM aspirate (SC count not mentioned)
Details of comparator	Total knee arthroplasty	HA sodium hyaluronate by intra-articular injection was used once a week for 5 times as a course of treatment	HA	Acetaminophen Orally 500 mg every 8 h for 6 months.
Details of outcome	• Knee Society Score • Radiological Imaging Outcomes	• WOMAC • SF-36	• VAS • WOMAC	• VAS • WOMAC • SF-36 • KSS • KSFS
Notes	-	-	-	-
Study ID	Freitag et al. 2019[14]	Baria et al. 2022[15]	Kaszynski et al. 2022[16]	Vega et al. 2015[17]
Study design	• Double Blinded Phase I/II trial (3 arm)	• RCT with computer generated block randomization; no	• RCT	• Phase I/II RCT

		concealment and no blinding none of the patients, investigators, or research staff was blinded		
Place of Study	-	-	Poland	Spain
Details of participants	• Radiological diagnosis of osteoarthritis using the American College of Rheumatology criteria. • Radiological grading of Grade II–III osteoarthritis (OA) of the knee as determined by a qualified radiologist using the Kellgren and Lawrence system. VAS Baseline: NA Age: Control :51.5 ± 6.1, Study arm 1: 54.6 ± 6.3 Study arm 2: 54.7 ± 10.2	• Age of 25-75 years Body mass index <40 kg/m^2, Symptomatic knee OA (primary and posttraumatic) • Radiographic evidence of OA in the target knee (K-L grades 1-4). VAS-ADL Baseline PRP: 50.10 ± 21.73 MFAT: 48.97 ± 22.46	• Symptomatic knee OA, the age between 45 and 65 years old, Kellgren–Lawrence OA grades from weak to moderate (K-L I–III). • Minimum visual analogue scale (VAS) pain score of 4 and the VAS pain score equal or less than 2 in the contralateral knee.	• Grade II-IV osteoarthritis, according to the K-L grading scale 2.
Exclusion criteria	• Have other causes of their knee symptoms suspected to be due to serious pathology such as tumours or referral from the hip or lumbar spine. • MRI confirmed displaced meniscal tear • MRI confirmed Grade IV chondral loss	• Isolated patellofemoral OA • 3+ effusion in the target knee (stroke test grading system) • Valgus or varus deformities >10 • Steroid injection in the target knee in the past 3 months • Visco supplementation in	• Use of local corticosteroids up to 3 months or hyaluronic acid injections up to 6 months before the treatment • Joint infections (present and past), 3. Previous knee arthroscopy surgery (up to 1 year)	• Signs of infection or positive serology for HIV, hepatitis, or syphilis • Congenital or acquired diseases leading to significant knee deformities that may interfere with cell application or the interpretation of results

	• Previous meniscectomy/ significant partial meniscectomy or other knee related surgery within the last 12 months	the target knee in the past 6 months • PRP in the target knee in the past 1 year	• Peripheral inflammatory diseases (e.g., rheumatoid arthritis, spondyloarthropathies)	• Pregnancy or breast-feeding • Immunosuppression.
Details of intervention	Autologous MSCs One-injection group: a single intra-articular injection of 100×10^6 ADMSCs	Autologous MFAT Single injection of MFAT or PRP	AAT PRP-Three injections, given a half month apart; AAT- One dose of final liposome product	Allogenic BM-MSCs injection given in medial para patellar area
Details of comparator	Conservative management only	PRP	PRP	HA
Details of outcome	• WOMAC • NPRS • KOOS	• VAS • KOOS • ADL • QoL	• WOMAC • Timed Up and Go Test • Maximal Voluntary Isometric Contraction (MVIC)	• VAS • WOMAC • Monitorization of articular cartilage quality.
Notes	Funded jointly by both Magellan Stem Cells and Melbourne Stem Cell Centre.	-	No external funding reported	-
Study ID	Kim et al. 2022[18]	Sadri et al. 2023[19]	Matas et al. 2019[20]	Lu et al. 2019[21]
Study design	Prospective, randomized, open-label, blind end-point (PROBE), 2-arm parallel, controlled trial	Phase II, triple-blinded, placebo controlled, randomized trial June 2019 and September 2021	Phase I/II randomized, double-blind, con-trolled trial	Prospective double-blind phase IIb RCT
Place of Study	Korea	Iran	Chile	China
Details of participants	Eligible patients were aged 20-80 years and had symptomatic medial	18 < Age < 65 Kellgren–Laurence grading: II or III.	Symptomatic knee OA (defined by daily pain at the affected joint for at least 3	The study included patients who were between 18 and 70years old, had a definite

	compartment knee OA [K-L] grades 2-4. VAS baseline: NA	visual analogue scale (VAS) equal or more than 3	months before inclusion) with grade 1–3 Kellgren-Lawrence radiographic changes in the targeted knee, without meniscal rupture. VAS (0-100) baseline: HA: 38.7 ± 19.4 UC-MSC 1: 44.8 ± 16.5 UC-MSC2: 39.4 ± 21.4	diagnosis of knee OA according to the American College of Rheumatology Clinical classification criteria for knee osteoarthritis Below grade 4 by K-L criteria. Age, mean: Study-55.03 (9.19), Control-59.64 (5.97)
Exclusion criteria	• Patients with measures twice or more than normal in lab test or with any condition that principal investigator considers clinically important. • Patients with serious condition which can affect this study such as cardiovascular diseases, renal diseases, liver diseases, endocrine diseases, cancer or diabetes. • Osteoporosis	• Uncontrolled diabetes (HbA1c > 8.5%) • Heart diseases (EF < 45%) • Allergy to proteins or cultured substances • Pregnancy or lactation • Concurrent corticosteroid therapy • Participating in another clinical trial	• Bilateral symptomatic knee OA, condylar or tibial plateau generalized bone marrow edema on MRI • Major axial deviation of the involved leg • Use of oral or intra-articular steroids or hyaluronic acid in the past 6 months • Ipsilateral hip or ankle pain, local or systemic infection, any form of secondary arthritis, previous malignancy, or body mass index≥30	• History of allergy or allergic constitution; • Concomitant severe infection, malignant tumor, coagulation disorder, or uncontrolled or unmanageable systemic diseases; • Presence of other types of arthritis except OA • Intraarticular injection of HA or corticosteroid in the preceding 2months
Details of intervention	ADMSC 1×10^8 MSCs in 3 mL of normal saline was	ADMSC A single injection of 100×10^6 AD-MSCs; 5 ml	Umbilical Cord-Derived Mesenchymal Stromal Cells Three groups- intra-	Autologous Adipose derived MPCs- 5×10^7haMPCs

	administrated.		articular knee injections of HA at baseline and 6 months UC-MSCs at baseline and 6 months, or UC-MSCs only at baseline, followed by placebo at 6 months MSC injections contained 20×10^6 UC-MSCs in 3 cc of saline with 5% AB plasma, HA injections contained 3 cc of Durolane, and placebo injections contained 5% AB plasma in 3 cc of saline	The haMPC group was injected with 5×10^7 haMPCs (around 2.5 ml) at weeks 0 and 3. Sham injection was performed at weeks 1 and 2.
Details of comparator	Medial open-wedge high tibial osteotomy	Normal Saline	HA	HA In the HA group, intra-articular injection of HA was administrated once a week, four consecutive weeks (week 0, 1, 2, and 3)
Details of outcome	• MOCART • MOAKS • WOMAC • KOOS • PROMs	• WOMAC • VAS • KOOS • SF36	• Safety • WOMAC • SF36 • OMERACT • Patient global assessment	• WOMAC • VAS • SF36
Notes	-	-	-	Cellular Biomedicine Group and the National Key Research and Development Program of China

Study ID	Emadedin et al. 2018[22]	Zhang s et al. 2022[23]	Zhang Y et al. 2022[24]	Bastos et al. 2020[25]
Study design	Triple blind RCT	Single centre, parallel group, assessor blinded, and randomized controlled clinical trial May 2013 to July 2015	Prospective double-blinded randomized study	Controlled, double-blind clinical trial permuted-blocks randomization.
Place of Study	Iran	China	-	-
Details of participants	Age 18-65, K-L grades 2,3,4, OA diagnosed using X-ray, no severe joint involvement for grade 4 OA, Angle of parenthesis feet not >20, WOMAC pain >25. VAS baseline: NA Age: Study: 51.7 ± 9.2 Control: 54.7 ± 5.3	Diagnosis met the diagnostic criteria in the American Rheumatism Association Revised Classification Criteria for Knee Osteoarthritis K-L grade 2–3. Baseline VAS: SVF: 4.04 ± 1.46 HA: 3.64 ± 0.98 Age 20–85 years. Age Study = 53.98 ± 13.69 control = 55.63 ± 12.18	18 and 70 years, with OA K-L grades 2 and 3, Initial pain evaluated at four or greater on a ten- point visual analog scale (VAS) in the knee joint	The inclusion criteria were patients over age 35 with knee OA (based on American College of Rheumatology criteria) and confirmatory radiographs, K–L grade 1–4, Baseline VAS: NA Age Study 30.6±4.5 Control-55.9±13.4
Exclusion criteria	• Malignancy • Organ failure • Uncontrolled chronic disease other than OA Allergic reaction to anaesthesia • Pregnancy or lactation	• Local infection of the knee joint • Systemic diseases such as blood disorders or diabetes; rheumatoid arthritis, gout, autoimmune disease, or malignancy in the past 5 years	• Secondary arthritis (for example, secondary knee OA, rheumatoid arthritis, gouty arthritis, and previous articular fractures) • Having problem with anesthesia (according to the American Society	• Chronic use of oral corticosteroid or immunosuppressive therapies • History or presence of malignant disorders and/or use of chemo-therapy • Infection or active

		• Prior injection or use of oral steroids within 3 weeks before screening • Knee surgery within 6 months before screening	of Anaesthesiologists score) • Contraindicating MRI examination • Other causes of knee pain such as diffuse edema, meniscus tear	wound in the knee area, history of severe trauma to the knee (post-traumatic OA)
Details of intervention	Autologous bone marrow derived MSC Each patient in the MSC group receive done intra-articular implantation of $40x10^6$ MSC in 5ml saline supplemented with 2% human serum albumin	Stromal vascular fraction (SVF) SVF= 5 ml, with an average count of 4.84±1.61 cells The patient was placed in the supine position with the knee straight. Local sterilization was performed. 5 ml of SVF was injected into the joint cavity via a superior lateral approach under sterile technique by percutaneous puncture with a disposable syringe once a month for a total of three times.	SVF 4 ml of SVF suspension was injected into the region of the cartilage defect	MSCs When reaching the desired number of 40×10^6, cells were suspended in 10 mL PBS supplemented with 2% human albumin in the MSC group
Details of comparator	NS	HA	HA	Corticosteroids
Details of outcome	• VAS • WOMAC	• VAS • WOMAC • MRI defect area • K-L grade increase	• K-L grade increase • Volume of cartilage defect and the volume of healthy cartilage • VAS • WOMAC	• KOOS • Cytokine analysis

			• WORMS • MORCART	
Notes	Royan institution	Zhejiang Provincial Natural Science Foundation of China, National Natural Science Foundation of China	National Natural Science Foundation of China and Zhejiang Medical and Health Science and Technology Project	No funding
Study ID	Zaffagnini et al. 2022[26]	Gupta et al. 2016[27]	Gupta et al. 2023[28]	Shapiro et al. 2017[29]
Study design	Single-blind RCT	Randomized, double-blind, multicentric, placebo-controlled, phase II November 2011 to November 2013	Randomized, double-blind, multicentre, placebo-controlled phase 3 study January 2019 to April 2021	Prospective, Single-Blind, Placebo-Controlled Trial Age: Median (range) 60 (42-68)
Place of Study	Italy	India	India	USA
Details of participants	18 and 75 years with symptomatic knee OA (K-L 1-4) VAS Pain at baseline: MF-AT: 6.6 ± 2.0 PRP: 6.2 ± 2.0	Males or females in the age range 40–70 years (both inclusive) Radiographic evidence of grade 2 to 3 osteoarthritis (OA) based on the Kellgren and Lawrence radiographic entry criteria. Baseline VAS: Study 1:60.9 ± 10.7 Study 2: 73.7 ± 15.2 Control 1: 61.0± 23.8 Study 3: 57.4 ± 29.0 Study 4: 46.6 ± 23.6	Male and female patients aged 40-65Y Body mass index \30 History of primary osteoarthritis of the knee characterized by pain, requiring the intake of analgesics, Radiograph of the knee joint showing evidence of grade 2 to 3 osteoarthritis based on the K-L classification. VAS at baseline: BM-MSC: 66.1 ±13.96	Long-standing bilateral knee pain from mild to moderate bilateral osteoarthritis despite conventional treatments such as activity modification, weight loss, physical therapy, analgesics, nonsteroidal anti-inflammatory drugs, or injection therapy for at least 6 weeks. K-L score less than 4. Baseline VAS:

		Control 2: 65.3 ± 23.8 Age Study 1: 58.10 ± 8.23 Study 2: 57.30 ± 9.45 Control 1: 54.90 ± 8.27 Study 3: 55.00 ± 6.72 Study 4: 54.00 ± 6.73 Control: 56.70 ± 5.19	Placebo: 65.0 ± 13.09	BMAC: 3.1 (0 to 8.1) Placebo: 2.9 (0 to 7.0)
Exclusion criteria	• Patients incapable of understanding or unwilling to follow the study protocol, • Participation in previous or concurrent trials (ongoing or completed within 3 months), • Surgical treatment for the same disease within 1 year, • Malignancy or metabolic or thyroid disorders, alcohol or drug (medication) abuse	• History of surgery or major trauma to the study joint • Arthroscopy on the study joint in the previous 12 months • Signs of active study joint inflammation and/or, if qualifying with OA of the knee, a large, bulging effusion of the study knee joint with the loss of normal contour of the joint at the screening visit or at the baseline examination • Patients who received intra-articular steroids or hyaluronan within the last 3 months • Infections in or around the knee	• History of surgery or major trauma to the examined joint • Arthroscopic surgery on the examined joint in the previous 12 month • Signs of active joint inflammation and/or large, bulging effusion with a loss of the normal contour of the joint at the screening visit or on the baseline examination • Acute exacerbation of the examined joint in the past 6 week • Use of intra-articular steroids or hyaluronan within the past 3 month	• Severe osteoarthritis (Kellgren-Lawrence grade 4) • Rheumatological or other systemic disease • Diabetes, malignancy, or infections
Details of	MF-AT	Human bone marrow	BM-MSC	Bone marrow aspirate

intervention	MF-AT (5 mL) was collected in a 10-mL syringe to be injected into the patient. The injection was performed through a classic lateral parapatellar approach using an 18-gauge needle, with the patient in the supine position and the knee in extension.	derived mesenchymal stem cells (HBM-MSC)	single intra-articular injection of 25 million BMMSCs suspended in 2 mL plus 2 ml HA	concentrate with platelet free plasma 15 ml BMAC injected in the randomly assigned knee. Both knees were aspirated before the injection
Details of comparator	PRP	Placebo	Placebo	Saline The contralateral knee was injected with 15 mL of sterile saline. Both knees were aspirated before the injection.
Details of outcome	• KOOS • VAS	• VAS • ICOAP • WOMAC-OA	• WOMAC • MRI findings using T2 mapping and cartilage volume	• ICOAP • VAS
Notes	-	Stempeutics Research Pvt Ltd	Alkem lab plus Stempeutics Research	Centre for Regenerative Medicine, Mayo Clinic
Study ID	Lamo-Espinosa et al. 2016[30]	Kuah et al. 2018[31]	Dulic et al. 2021[32]	Lamo -Espinosa et al. 2018[33]
Study design	Phase I/II randomized clinical trial (3 arms)	Randomized, double-blind, single-centre, placebo-controlled, single ascending dose Phase I study (3 arm) April 2015 to March 2017	A single-center, prospective clinical trial with three study arms. April 2016 to December 2017	long-term follow up of a multicentre randomized controlled clinical trial (phase I/II)

Place of Study	-	Australia	-	-
Details of participants	Males and females aged 50–80, diagnosis of knee OA according to American College of Rheumatology criteria VAS joint pain ≥2.5, Kellgren–Lawrence radiological classification scale ≥2.	Males or females aged 40–65years, Diagnosed K-L grade 1, 2 or 3 knee OA in the study knee. moderate-severe pain in the study knee, 35–90 mm on a 100 mm visual analogue scale (VAS). Age: Study 1: 55.0 ± 5.15 Study 2: 50.8 ± 7.29 Control: 55.0 ±10.42	Adult patients with symptomatic knee. OA, Kellgren-Lawrence grade from 2 to 4 with symptoms for at least 12 months.	Males and females aged 50–80, diagnosis of knee OA according to American College of Rheumatology criteria, visual analogue scale (VAS) joint pain ≥2.5, K–L radiological classification scale ≥2.
Exclusion criteria	• Previous diagnosis of polyarticular disease, severe mechanical extra-articular deformation • Systemic autoimmune rheumatic disease, arthroscopy or intraarticular infiltration in the last 6 months • Chronic treatment with immunosuppressive or anticoagulant drugs, corticosteroids treatment in the 3 last months, nonsteroidal anti-inflammatory drugs	• Inability or unwillingness to comply with protocol requirements • Evidence, or diagnosis, of OA in the non-study knee that is of a worse screening visit VAS score than the study knee Joint • Surgery in the study knee, including arthroscopy, within the last 3years • Consistently occurring major mechanical issues in the study knee including locking, catching and giving way	• Knee instability • Severe misalignment, • Inflammatory arthritis such as rheumatoid arthritis and ankylosing spondylitis, and • Underlying diseases such as hematologic disorders, septicemia, coagulopathy, neoplasm, active infection, and immune deficiency.	• Previous diagnosis of polyarticular disease, severe mechanical extra-articular deformation • Systemic autoimmune rheumatic disease, arthroscopy or intraarticular infiltration in the last 6 months • Chronic treatment with immunosuppressive or anticoagulant drugs, corticosteroids treatment in the 3 last months, nonsteroidal anti-inflammatory drugs therapy in the last 15

	therapy in the last 15 days • Bilateral knee OA requiring treatment in both knees			days. • Bilateral knee OA requiring treatment in both knees
Details of intervention	BM-MSC plus HA intra-articular injection of 10×10^6autologous cultured BM-MSC in 1.5mlRinger's lactate solution OR 100×10^6 autologous cultured BM-MSC in 3ml Ringer's lactate solution followed by an intraarticular injection of 4ml HA.	MSC	BMAC	BM-MSC plus HA intra-articular injection of 10×10^6autologous cultured BM-MSC in 1.5ml Ringer's lactate solution OR 100×10^6 autologous cultured BM-MSC in 3ml Ringer's lactate solution followed by an intraarticular injection of 4ml HA.
Details of comparator	HA Control group, constituted by patients who received a single intra-articular injection of 60 mg HA (Hyalone®) in a final volume of 4ml	Cell culture media and cryopreservative	PRP/HA	HA Control group, constituted by patients who received a single intra-articular injection of 60mg HA (Hyalone®) in a final volume of 4ml
Details of outcome	• VAS • WOMAC	• VAS • WOMAC • Quantitative MRI assessments	• VAS • KOOS • WOMAC • IKDC	• VAS • WOMAC
Notes	EMV is supported by Network Center for Regenerative Medicine and Cellular Therapy of Castilla	Regeneus Ltd	Funding –not mentioned	Funding –not mentioned

	y León, Ministry of Health, Junta de Castilla y León.			
Study ID	Hong et al. 2018[34]	Carvalho Schweich-Adami et al. 2022[35]	Sadat-Ali et al. 2021[37]	Hernigou et al. 2020[38]
Study design	Double-blind randomized self-controlled trial	Open label RCT	Prospective, open-label, single-dose, RCT	Prospective randomized study
Place of Study	China	Brazil	Saudi Arabia	-
Details of participants	Age 18–70 years old, Bilateral knees with Grade II-III osteoarthritis, identified by two different observers, according to the Kellgren-Lawrence grading scale. Bilateral knees with initial pain evaluated at four or greater on a ten-point VAS	Adult individuals, of both genders, aged between 40 and 75 years with a diagnosis of OA grade II to IV (K-L). significant for PRP, ADSCs + PRP and ADSCs groups. In Control group, the initial score was 6.3±1.15 and in PRP it was 7.6±1.57. ADSCs+PRP it was 8.6± 1.1. ADSCs it was8.9 ±1.10. Age: Control: 41 ± 4.67 PRP: 48 ± 3.51 ADSC+PRP:52.66 ± 4.60 ADSC :58.5 ± 6.17	Age 45 and 70 years, diagnosed with OAK for at least 12 months based on American College of Rheumatology (ACR) criteria, and unsatisfied with conservative therapy of NSAIDs and physiotherapy Age Study: 56.18±6.56 Control: 56.75±5.77	This study included 140 adults aged 65 to 90 years who had comparable pain in both knees. K-L Grade 2 to 4. VAS pain score Baseline Cell therapy: 4.43 (0.54) TKA: 3.4 (2 to 6) Age: (mean, range) 75.4 years (65–90)
Exclusion criteria	• History of liposarcoma and other cancer • Pregnancy, Immunosuppression, Coagulopathy, Abdominal hernia • Any knee joint	• Individuals with hemophilia, anaemia • Gastrointestinal diseases, cancer, thyroid disorders, liver, previous nephrology • Acquired	• Past knee intra-articular steroid/hyaluronic acid injection within the last 3 months • Any knee surgery within the last 6	Not mentioned

	operation or intra-articular injection of any drug within 6 months before the screening, • Sign of infection or serological positive of HIV, syphilis • A low level of body fat content that may make liposuction difficult	Immunodeficiency Syndrome (AIDS).	months • Pregnancy and breast-feeding • Mental disorders and drug de-pendency.	
Details of intervention	Adipose-derived stromal vascular fraction (AD SVF) single IA injection of SVF 4 ml	Adipose-derived stem cells. The patient received local anesthesia (2% lidocaine) in the lateral interarticular region of the knee. After 10 min, transplantation was performed through an intra-articular injection (21G needle) of ADSCs in the affected knee	Autologous Bone Marrow Derived Chondrocytes Cell suspension was injected intra-articularly in the affected joint as a single-dose injection	MSC Treatment was performed by percutaneous injection of 20mL BMC in the subchondral medial femorotibial compartment of each knee, i.e., 10mL in the medial tibial plateau and 10mL in the medial condyle
Details of comparator	HA Single IA injection of HA 4 ml	PRP Before transplantation, the patient's knee was submitted to asepsis and then the intra-articular injection of PRP was performed	NSAIDs and physical therapy as needed	TKA
Details of outcome	• WOMAC • WORMS • MOCART	• VAS • SF36 • WOMAC	• K-L grading • VAS • MKSSSF	• Cartilage volume changes over time

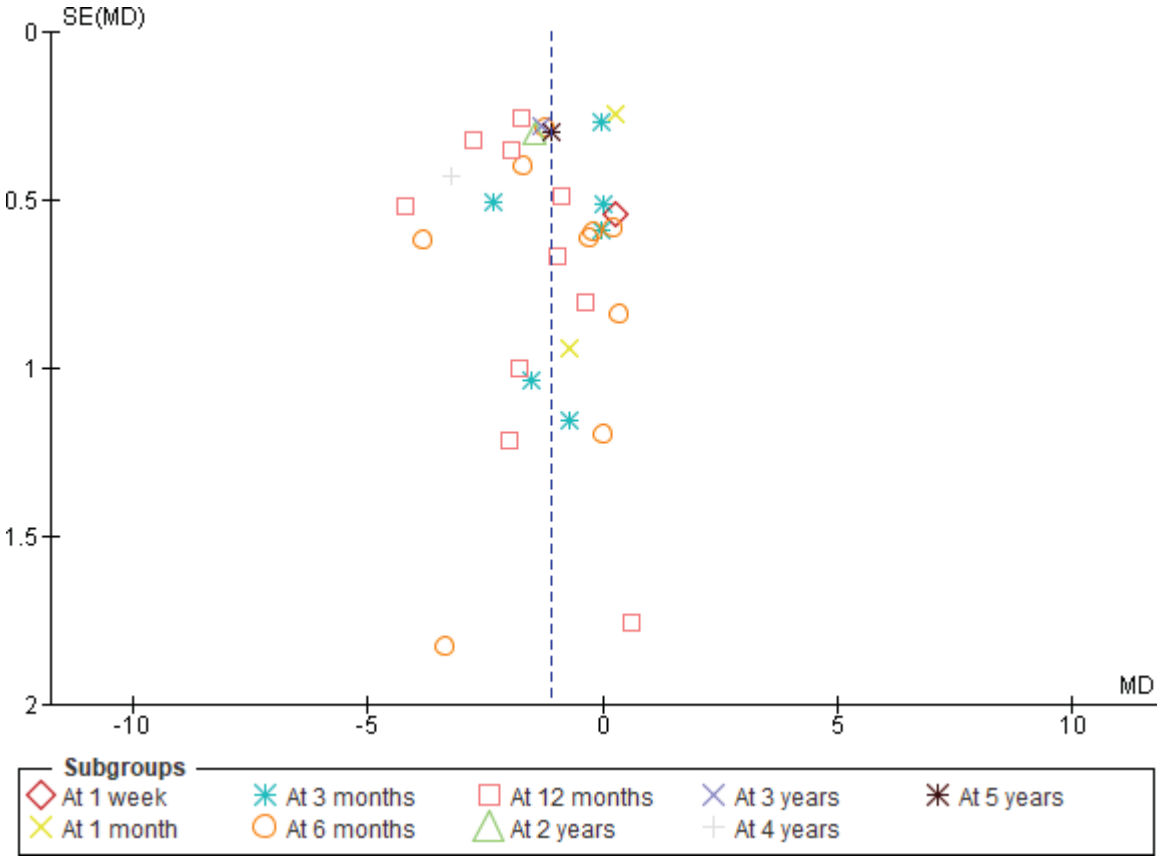
		• Synovial Fluid analysis	• QoL	
Notes	National Natural Science Foundation of China and Medical Science and Technology Foundation of Zhejiang Province	Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), Brasil; Fundação de ApoioaoDesenvolvimento do Ensino, Ciência e Tecnologia do Estado de Mato Grosso do Sul (FUNDECT), Brasil	Funding: not mentioned	Funding – not mentioned
Study ID	Garza et al. 2020[39]		Zhou et al. 2021[9]	
Study design	A Double-Blinded Prospective Randomized Controlled Clinical Trial (3 arm)		RCT April 2018 to December 2019	
Place of Study	-		China	
Details of participants	Men and non-pregnant women between the age of 40 and 75. Grade 2 or 3 Kellgren-Lawrence OA on radiograph. Baseline VAS: NA Age: Control: 57.1 +/- 9.1 (41-74) Low dose group: 60.5+/-7.9 (48-71) High dose group: 59.5+/-11.7 (41-74)		Age between 18and 75 years old, presence of clearly indicated articular cartilage lesions on MRI and Kellgren-Lawrence grade ≤level 3. Age Study: 52.27±1.17 Control:51.77±7.55	
Exclusion criteria	• A body mass index>35, • American Society of Anesthesiologists score>3 • History of symptomatic OA (hips, spine, or ankle), rheumatologic disease, avascular necrosis, severe bone deformity, previous infection of the knee joint		• Symptoms and imaging findings localized in the patellofemoral joint • Presence of malignant neoplasms • Active infection anywhere in the body, • Articular cartilage lesions caused by infectious or gouty arthritis • Presence of autoimmune diseases such as rheumatoid arthritis or ankylosing spondylitis	
Details of	Mesenchymal Stromal cells		Knee arthroscopic therapy with autologous IPFP	

intervention	The dose-escalated Study used a parallel-group design with 3 arms: high-dose treatment group ($3.0x10^7$ SVF cells), low-dose treatment group ($1.5x10^7$ SVF cells), and placebo control group (zero SVF cells)	(infrapatellar fat pad) cell concentrates 5mL of the cell concentrates was injected into the corresponding joint cavity
Details of comparator	Placebo	Regular knee arthroscopic therapy
Details of outcome	• WOMAC • MRI Review	• WOMAC • VAS • MOCART
Notes	The GID Group provided funding for all supplies related to the clinical trial. The GID Group also provided funding for data collection personnel	National Key Research Development Plan

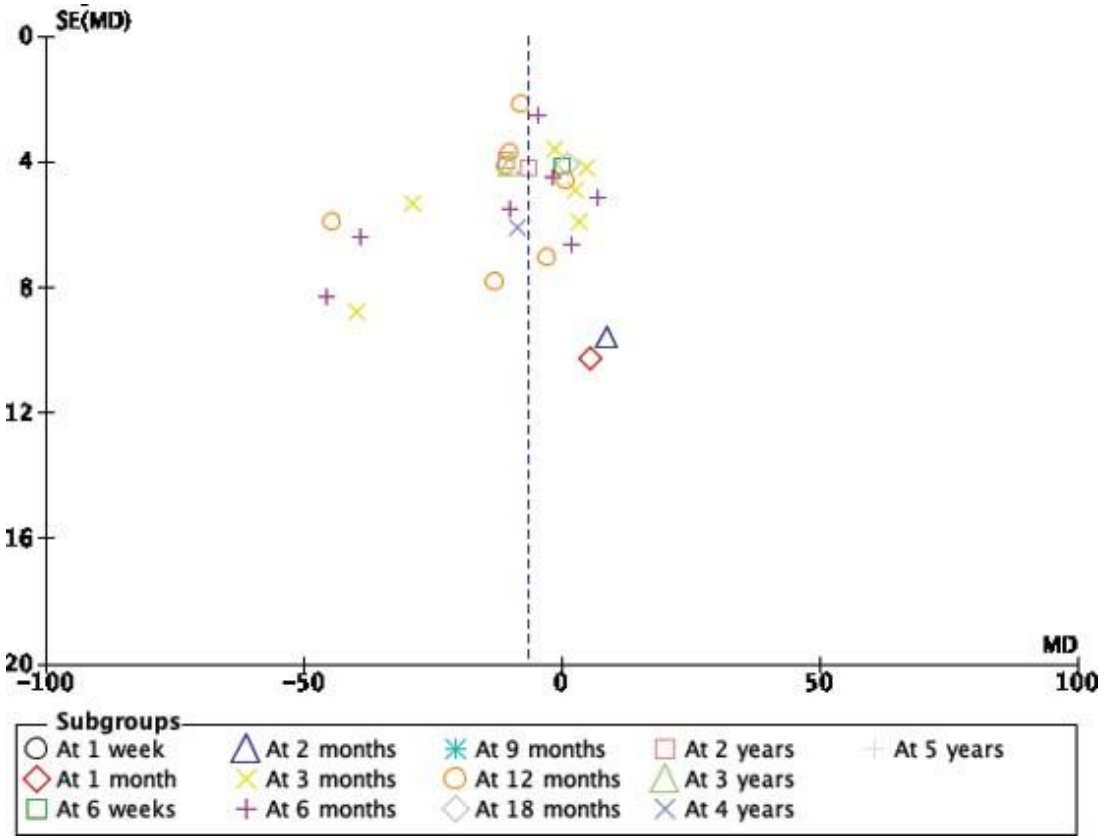
viii. Publication bias:

Overall bias due to publication was regarded as low for current review. We did not carry out formal publication bias assessment for individual outcome-timepoint because of less than studies for each outcome at any given time point. However, we have attached the funnel plots for some of the outcomes for subjective interpretation.

Funnel plot for VAS



Funnel plot for WOMAC



ix. List of Excluded Studies:

TITLE	REASON FOR EXCLUSION
Matrix-induced autologous mesenchymal stem cell implantation versus matrix-induced autologous chondrocyte implantation in the treatment of chondral defects of the knee: a 2-year randomized study	wrong population
Adipose derived mesenchymal stem cell therapy in the treatment of isolated knee chondral lesions: design of a randomised controlled pilot study comparing arthroscopic microfracture versus arthroscopic microfracture combined with postoperative mesenchymal stem cell injections	wrong population
Transplantation of autologous bone marrow-derived mesenchymal stem cells under arthroscopic surgery with microfracture versus microfracture alone for articular cartilage lesions in the knee: A multicenter prospective randomized control clinical trial	wrong population
Inefficacy of autologous bone marrow concentrate in stage three osteonecrosis: a randomized controlled double-blind trial	wrong population

Adipose-derived mesenchymal stem cells with microfracture versus microfracture alone: 2-year follow-up of a prospective randomized trial	wrong population
Platelet-rich plasma and adipose-derived mesenchymal stem cells in association with arthroscopic microfracture of knee articular cartilage defects: a pilot randomized controlled trial	wrong population
Allogenic umbilical cord blood-derived mesenchymal stromal cell implantation was superior to bone marrow aspirate concentrate augmentation for cartilage regeneration despite similar clinical outcomes	wrong population
Allogeneic umbilical cord blood-derived mesenchymal stem cells implantation for large cartilage defects in older patients	wrong population
Allogeneic umbilical cord blood-derived mesenchymal stem cells versus microfracture for large full-thickness cartilage defects	wrong population
Follow-up study of cartistemâ® versus microfracture for the treatment of knee articular cartilage injury or defect	wrong population
Study to compare efficacy and safety of cartistem and microfracture in patients with knee articular cartilage injury	wrong population
Replenishing cartilage from endogenous stem cells	wrong population
Tissue engineering, embryonic, organ and other tissue specific stem cells: scaffold-free pellet-type autologous chondrocyte implantation (CARTILIFEÂ®) for for the restoration of articular cartilage defects: a randomized phase 2 clinical trial and extended 5-year clinical follow-up	wrong population
Shockwave therapy combined with autologous adipose-derived mesenchymal stem cells is better than with human umbilical cord wharton's jelly-derived mesenchymal stem cells on knee osteoarthritis	wrong population
Keynote: Human articular cartilage repair using umbilical cord blood derived allogenic mesenchymal stem cells	wrong population
2012 ACR/ARHP Annual scientific meeting late-breaking abstracts	wrong population
Autologus micro-fragmented adipose tissue for the treatment od diabetic foot minor amputations: a randomized controlled single-center clinical trial (MiFrAADif)	wrong population
Activated platelet-rich plasma improves cartilage regeneration using adipose stem cells encapsulated in a 3D alginate scaffold	wrong population
Identification of human temporomandibular joint fibrocartilage stem cells with distinct chondrogenic capacity	wrong population
Stem cell therapy for osteonecrosis of the femoral head	wrong population
Novel biologically-inspired rosette nanotube PLLA scaffolds for improving human mesenchymal stem cell chondrogenic differentiation	wrong population
Effects of hypoxia on osteogenic differentiation of mesenchymal stromal cells used as a cell therapy for avascular necrosis of the femoral head	wrong population
Integrative analysis reveals CD38 as a therapeutic target for plasma cell-rich pre-disease and established rheumatoid arthritis and systemic lupus erythematosus	wrong population

Enhanced tibial osteotomy healing with use of bone grafts supplemented with platelet gel or platelet gel and bone marrow stromal cells	wrong population
Î±10hi MSCs decrease synovial membrane long term expression of TIMP-2 and NFÎºB following articular injury	wrong population
The recombinant Link module of human TSG-6 suppresses cartilage damage in models of osteoarthritis: A potential disease-modifying OA drug	wrong population
Monocytes from patients with osteoarthritis display increased osteoclastogenesis and bone resorption: The in vitro osteoclast differentiation in arthritis study	wrong population
Comparative efficacy of endogenous stem cells recruiting hydrogels and stem cell-loaded hydrogels in knee cartilage regeneration: a meta-analysis	wrong population
Effects of Conditioned Medium From Osteoarthritic Cartilage Fragments on Donor-Matched Infrapatellar Fat Pad-Derived Mesenchymal Stromal Cells	wrong population
Ten-year results of mesenchymal stromal cell transplantation augmented with vascularised bone grafts for advanced osteonecrosis of the femoral head	wrong population
Intra-articular injections of allogeneic mesenchymal stromal cells vs. high molecular weight hyaluronic acid in dogs with osteoarthritis: exploratory data from a double-blind, randomized, prospective clinical trial	wrong population
Synovial mesenchymal stem cells from osteo- or rheumatoid arthritis joints exhibit good potential for cartilage repair using a scaffold-free tissue engineering approach	wrong population
CD10-bound human mesenchymal stem/stromal cell-derived small extracellular vesicles possess immunomodulatory cargo and maintain cartilage homeostasis under inflammatory conditions	wrong population
Early-stage osteonecrosis of the femoral head: where are we and where are we going in year 2018?	wrong population
10-year follow-up results of the prospective, double-blinded, randomized, controlled study on autologous bone marrow buffy coat grafting combined with core decompression in patients with avascular necrosis of the femoral head	wrong population
Treatment with human adipose-derived mesenchymal stem cells for knee OA: evidences from a randomized and double-blinded phase I/II a clinical trial	wrong population
Allogeneic mesenchymal stem cells for the treatment of arthrosis and disc degeneration. Does hla identity affect it effectiveness?	wrong population
Human amniotic mesenchymal stromal cells as favorable source for cartilage repair	wrong population
Equine umbilical cord mesenchymal stem cells demonstrate safety and efficacy in the treatment of canine osteoarthritis: a randomized placebo-controlled trial	wrong population
Elevated Levels of Soluble ST2 were Associated with Rheumatoid Arthritis Disease Activity and Ameliorated Inflammation in Synovial Fibroblasts	wrong population

NSAIDs reduce therapeutic efficacy of mesenchymal stromal cell therapy in a rodent model of posttraumatic osteoarthritis	wrong population
In vitro characterization of bone marrow stromal cells from osteoarthritic donors	wrong population
Combined use of adipose derived stem cells and TGF-Î²3 microspheres promotes articular cartilage regeneration in vivo	wrong population
A static magnetic field enhances the repair of osteoarthritic cartilage by promoting the migration of stem cells and chondrogenesis	wrong population
DFATs derived from infrapatellar fat pad hold advantage on chondrogenesis and adipogenesis to evade age mediated influence	wrong population
Comparison of methods for the isolation and culture of Migratory chondroprogenitors from Human articular cartilage	wrong population
Engineering osteoarthritic cartilage model through differentiating senescent human mesenchymal stem cells for testing disease-modifying drugs	wrong population
Safety, tolerability, clinical, and joint structural outcomes of a single intra-articular injection of allogeneic mesenchymal precursor cells in patients following anterior cruciate ligament reconstruction: a controlled double-blind randomised trial	wrong population
Clinical and radiological comparison of single and double intra-articular injection of adipose-derived stromal vascular fraction for knee osteoarthritis	wrong study design
Intra-articular injection of bone marrow aspirate concentrate (BMAC) or adipose-derived stem cells (ADSCs) for knee osteoarthritis: a prospective comparative clinical trial	wrong study design
Allogenic umbilical cord blood-derived mesenchymal stromal cell implantation was superior to bone marrow aspirate concentrate augmentation for cartilage regeneration despite similar clinical outcomes	wrong study design
Clinical safety and effectiveness of adipose-derived stromal cell vs stromal vascular fraction injection for treatment of knee osteoarthritis: 2-year results of parallel single-arm trials	wrong study design
Vast potential for clinical trial opportunities; adipose tissue derived mesenchymal stem cells	wrong study design
Effect of platelet-rich plasma injections on cartilage t1rho in knee osteoarthritis	wrong study design
Mesenchymal progenitor cells from non-inflamed versus inflamed synovium post-ACL injury present with distinct phenotypes and cartilage regeneration capacity	wrong study design
Clinical results and second-look arthroscopic findings after treatment with adipose-derived stem cells for knee osteoarthritis	wrong study design
Knee osteoarthritis: clinical and mri outcomes after multiple intra-articular injections with expanded autologous adipose-derived stromal cells or platelet-rich plasma	wrong study design
Comparison of the Effect of MFAT and MFAT + PRP on Treatment of Hip Osteoarthritis: An Observational, Intention-to-Treat Study at One Year	wrong study design

Age and synovitis affect the results of the treatment of knee osteoarthritis with Micro fragmented Autologous Fat Tissue	wrong study design
Safety of an allogeneic, human, umbilical cord blood-derived mesenchymal stem cells-4% hyaluronate composite for cartilage repair in the knee	wrong study design
Patient-Reported Outcomes After Platelet-Rich Plasma, Bone Marrow Aspirate, and Adipose-Derived Mesenchymal Stem Cell Injections for Symptomatic Knee Osteoarthritis	wrong study design
Combination of intra-articular autologous activated peripheral blood stem cells with growth factor addition/ preservation and hyaluronic acid in conjunction with arthroscopic microdrilling mesenchymal cell stimulation Improves quality of life and regenerates articular cartilage in early osteoarthritic knee disease	wrong study design
Intraarticular injections of mesenchymal stem cells in knee osteoarthritis	wrong study design
Comparative clinical observation of arthroscopic microfracture in the presence and absence of a stromal vascular fraction injection for osteoarthritis	wrong study design
Comparison between total knee arthroplasty and MCIC (autologous bone marrow mesenchymal-cell-induced-chondrogenesis) for the treatment of osteoarthritis of the knee	wrong study design
Erratum to: Comparison between total knee arthroplasty and MCIC (autologous bone marrow mesenchymal-cell-induced-chondrogenesis) for the treatment of osteoarthritis of the knee [Tissue Engineering and Regenerative Medicine, 11, 5, (2014) 405-413, DOI 10.1007/s13770-014-0041-8]	wrong study design
Safety of an allogeneic, human, umbilical cord blood-derived mesenchymal stem cells-4% hyaluronate composite for cartilage repair in the knee	wrong study design
Bone marrow mesenchymal stromal cell treatment in patients with osteoarthritis results in overall improvement in pain and symptoms and reduces synovial inflammation	wrong study design
A single dose of Bone Marrow Mononuclear Cells (BMMNCs) and Bone Marrow Plasma Concentrate (BMPC) for the treatment of Knee OA. 12 months of follow up	wrong study design
The influence of adipose-derived stromal vascular fraction cells on the treatment of knee osteoarthritis	wrong study design
Gene expression and functional comparison between multipotential stromal cells from lateral and medial condyles of knee osteoarthritis patients	wrong study design
Implantation of Allogenic Mesenchymal Stem Cell from Umbilical Cord Blood for Osteoarthritis Management	wrong study design
Mesenchymal stem cell transplantation for osteoarthritis	wrong study design
Development of autologous platelet-rich plasma mixed-microfat as an advanced therapy medicinal product for intra-articular injection of radio-carpal osteoarthritis: from validation data to preliminary clinical results	wrong study design
Infrapatellar fat pad-derived mesenchymal stem cell therapy for knee	wrong study design

osteoarthritis	
Comparison of exosomes secreted by induced pluripotent stem cell-derived mesenchymal stem cells and synovial membrane-derived mesenchymal stem cells for the treatment of osteoarthritis	wrong study design
Increased serum fibroblast growth factor-23 (FGF-23) and bone turnover in patients with osteoarthritis of knee	wrong study design
Novel Use of Intraarticular Granulocyte Colony Stimulating Factor (hG-CSF) Combined with Activated Autologous Peripheral Blood Stem Cells Mobilized with Systemic hG-CSF: Safe and Efficient in Early Osteoarthritis	wrong study design
Mesenchymal Stem Cells in a Clinical Trial to Heal Articular Cartilage Defects	wrong study design
A prospective case series of patients treated with adult autologous, culture-expanded mesenchymal stem cells for symptomatic osteoarthritic hip and knee joints compared to an untreated comparison group	wrong study design
Intradiscal injections of orthobiologics	wrong study design
Future trends for unicompartmental arthritis of the knee: lnjectables & stem cells	wrong study design
treatment of osteoarthritis with mesenchymal stem cells	wrong study design
Human umbilical cord-blood-derived mesenchymal stem cell can improve the clinical outcome and joint space width after high tibial osteotomy	wrong study design
Comparative clinical outcomes after intra-articular injection with adipose-derived cultured stem cells or noncultured stromal vascular fraction for the treatment of knee osteoarthritis	wrong study design
Functional outcomes following micro fragmented adipose tissue versus bone marrow aspirate concentrate injections for symptomatic knee osteoarthritis	wrong study design
Alterations in cartilage quantification before and after injections of mesenchymal stem cells into osteoarthritic knees	wrong study design
Prospective study comparing leukocyte-poor platelet rich plasma combined with hyaluronic acid and autologous microfragmented adipose tissue in patients with early knee osteoarthritis	wrong study design
Five-year outcome of 1-stage cell-based cartilage repair using recycled autologous chondrons and allogenic mesenchymal stromal cells: a first-in-human clinical trial	wrong study design
Temporomandibular joint arthrocentesis and microfragmented adipose tissue injection for the treatment of internal derangement and osteoarthritis: a randomized clinical trial	wrong study design
Autologous matrix-induced chondrogenesis plus peripheral blood concentrate (AMIC+PBC) in chondral defects of the first metatarsophalangeal joint	wrong study design
Long-term efficacy of autologous bone marrow mesenchymal stromal cells for treatment of knee osteoarthritis	wrong study design
Stem cell-based therapeutic strategies for cartilage defects and osteoarthritis	wrong study design
Osteoclast differentiation and bone resorption in multicentric reticulohistiocytosis	wrong study design

Biological Therapies in Regenerative Sports Medicine	wrong study design
Repeated intra-articular injections of umbilical cord-derived mesenchymal stem cells for knee osteoarthritis: a phase I, single-arm study	wrong study design
Associations of Symptomatic Knee Osteoarthritis With Histopathologic Features in Subchondral Bone	wrong study design
Stem cells in degenerative orthopaedic pathologies: effects of aging on therapeutic potential	wrong study design
Intra-articular injection in the knee of adipose derived stromal cells (stromal vascular fraction) and platelet rich plasma for osteoarthritis	wrong study design
Technology evaluation: MFG-IRAP, University of Pittsburgh	wrong study design
Concise Review: Using Fat to Fight Disease: A Systematic Review of Nonhomologous Adipose-Derived Stromal/Stem Cell Therapies	wrong study design
Identification of human temporomandibular joint fibrocartilage stem cells with distinct chondrogenic capacity	wrong study design
Autologous adipose stem cell therapy for knee osteoarthritis: where are we now?	wrong study design
A 24-month follow-up study of the effect of intra-articular injection of autologous microfragmented fat tissue on proteoglycan synthesis in patients with knee osteoarthritis	wrong study design
Changes in Chondrogenic Progenitor Populations Associated with Aging and Osteoarthritis	wrong study design
Genicular nerve radiofrequency ablation for the treatment of avascular necrosis knee pain	wrong study design
Cell-based therapy approaches: the hope for incurable diseases	wrong study design
Mesenchymal Stem cells: A new choice for nonsurgical treatment of oa? results from a bayesian network meta-analysis	wrong study design
Percutaneous injection of autologous, culture-expanded mesenchymal stem cells into carpometacarpal hand joints: A case series with an untreated comparison group	wrong study design
[Therapeutic utilization of stem cells in orthopedics]	wrong study design
Enriched Peripheral Blood-Derived Mononuclear Cells for Treating Knee Osteoarthritis	wrong study design
Allogeneic umbilical cord blood-derived mesenchymal stem cells combined with high tibial osteotomy: a retrospective study on safety and early results	wrong study design
Clinical and cost-effectiveness of autologous chondrocyte implantation for cartilage defects in knee joints: systematic review and economic evaluation	wrong study design
Culture-expanded mesenchymal stromal cell therapy: does it work in knee osteoarthritis? A pathway to clinical success	wrong study design
Efficacy of mesenchymal stem cells in treating patients with osteoarthritis of the knee: A meta-analysis	wrong study design
Research trends of platelet-rich plasma therapy on knee osteoarthritis from 2011 to 2021: A review	wrong study design
Evaluation of apoptosis induction in human peripheral blood mononuclear	wrong study design

cells and synovial cells in patients with rheumatoid arthritis	
Umbilical Cord-Derived Stem Cells for the Treatment of Knee Osteoarthritis: A Systematic Review	wrong study design
Regarding â€œIntra-Articular Injections of Hyaluronic Acid or Steroid Associated with Better Outcomes Than Platelet-Rich Plasma, Adipose Mesenchymal Stromal Cell, or Placebo in Knee Osteoarthritis: A Network Meta-analysisâ	wrong study design
Umbilical cord-derived mesenchymal stem cells for treating osteoarthritis of the knee: a single-arm, open-label study	wrong study design
Efficacy and Safety of Intra-Articular Cell-Based Therapy for Osteoarthritis: Systematic Review and Network Meta-Analysis	wrong study design
C1q/TNF-related protein-9 suppresses inflammation in synovial cells from patients with osteoarthritis	wrong study design
Sodium hyaluronate therapy in osteoarthritis: Arguments for a potential beneficial structural effect	wrong study design
Intraarticular injection of bone marrow-derived mesenchymal stem cells enhances regeneration in knee osteoarthritis	wrong study design
Current evidence on mesenchymal stem cells for hip osteoarthritis: a narrative review	wrong study design
Failures, Reoperations, and Improvement in Knee Symptoms Following Matrix-Assisted Autologous Chondrocyte Transplantation: A Meta-Analysis of Prospective Comparative Trials	wrong study design
Comparative efficacy of endogenous stem cells recruiting hydrogels and stem cell-loaded hydrogels in knee cartilage regeneration: a meta-analysis	wrong study design
Mesenchymal stem cells for the treatment of cartilage lesions: from preclinical findings to clinical application in orthopaedics	wrong study design
Evaluation of autologous adipose-derived mesenchymal stem cell therapy in focal chondral defects of the knee: A pilot case series	wrong study design
Alternative and complementary therapies in osteoarthritis and cartilage repair	wrong study design
Effect of Combined Intraosseous and Intraarticular Infiltrations of Autologous Platelet-Rich Plasma on Subchondral Bone Marrow Mesenchymal Stromal Cells from Patients with Hip Osteoarthritis	wrong study design
Biological approaches for cartilage repair	wrong study design
One-Stage Cartilage Repair Using a Hyaluronic Acid-Based Scaffold With Activated Bone Marrow-Derived Mesenchymal Stem Cells Compared With Microfracture: Five-Year Follow-up	wrong study design
Long-term effect of nonsteroidal anti-inflammatory drugs on the production of cytokines and other inflammatory mediators by blood cells of patients with osteoarthritis	wrong study design
Assessment of clinical, biochemical, and radiological outcomes following	wrong study design

intra-articular injection of Wharton jelly-derived mesenchymal stromal cells in patients with knee osteoarthritis: A prospective clinical study	
Evaluation of umbilical cord derived Wharton's jelly for regenerative medicine applications	wrong study design
Clinical therapeutic efficacy of mesenchymal stem cells derived from adipose or bone marrow for knee osteoarthritis: A meta-analysis of randomized controlled trials	wrong study design
Clinical efficacy and safety of stem cell therapy for knee osteoarthritis: A meta-analysis	wrong study design
What is the optimal dose of adipose-derived mesenchymal stem cells treatment for knee osteoarthritis? A conventional and network meta-analysis of randomized controlled trials	wrong study design
The effect of intra-articular injection of autologous microfragmented fat tissue on proteoglycan synthesis in patients with knee osteoarthritis	wrong study design
Regarding â€œIntra-Articular Injections of Hyaluronic Acid or Steroid Associated With Better Outcomes Than Platelet-Rich Plasma, Adipose Mesenchymal Stromal Cell, or Placebo in Knee Osteoarthritis: A Network Meta-analysisâ€	wrong study design
Synovial tissue-infiltrating natural killer cells in osteoarthritis and periprosthetic inflammation	wrong study design
Interleukin-34 produced by human fibroblast-like synovial cells in rheumatoid arthritis supports osteoclastogenesis	wrong study design
Effectiveness of mesenchymal stem cells for treating patients with knee osteoarthritis: a meta-analysis toward the establishment of effective regenerative rehabilitation	wrong study design
Clinical use of stem cells in orthopaedics	wrong study design
The role of adipose-derived mesenchymal stem cells in knee osteoarthritis: a meta-analysis of randomized controlled trials	wrong study design
Advances in stem cell therapy for cartilage regeneration in osteoarthritis	wrong study design
Effectiveness of treatment with mesenchymal stem cells of adipose tissue (lipogems) in patients with bilateral gonarthrosis. about a case	wrong study design
Increased expression of human type IIa secretory phospholipase A2 antigen in arthritic synovium	wrong study design
Impact of changes in clinical practice guidelines for intra-articular injection treatments for knee osteoarthritis on public interest and social media	wrong study design
Does the Source of Mesenchymal Stem Cell Have an Effect in the Management of Osteoarthritis of the Knee? Meta-Analysis of Randomized Controlled Trials	wrong study design
Does vehicle-based delivery of mesenchymal stromal cells give superior results in knee osteoarthritis? Meta-analysis of randomized controlled trials	wrong study design
Intra-articular Injection of Mesenchymal Stem Cells for the Treatment of Osteoarthritis of the Knee: A 2-Year Follow-up Study	wrong study design
Comparative analysis of gene expression between articular cartilage-derived to assess suitability of fibronectin adhesion assay to enrich cells	wrong study design

chondroprogenitors	
The treatment of focal chondral lesions of the knee	wrong study design
Bone Marrow Aspirate Concentrate: Its Uses in Osteoarthritis	wrong study design
Mesenchymal stem cell implantation in osteoarthritic knees: is fibrin glue effective as a scaffold?	wrong study design
Injection of Mesenchymal Stem Cells as a Supplementary Strategy of Marrow Stimulation Improves Cartilage Regeneration after Lateral Sliding Calcaneal Osteotomy for Varus Ankle Osteoarthritis: Clinical and Second-Look Arthroscopic Results	wrong study design
Comparative Matched-Pair Analysis of Open-Wedge High Tibial Osteotomy With Versus Without an Injection of Adipose-Derived Mesenchymal Stem Cells for Varus Knee Osteoarthritis: Clinical and Second-Look Arthroscopic Results	wrong study design
Comparative Matched-Pair Analysis of the Injection Versus Implantation of Mesenchymal Stem Cells for Knee Osteoarthritis	wrong study design
Additional mesenchymal stem cell injection improves the outcomes of marrow stimulation combined with supramalleolar osteotomy in varus ankle osteoarthritis: short-term clinical results with second-look arthroscopic evaluation	wrong study design
Comparative outcomes of open-wedge high tibial osteotomy with platelet- rich plasma alone or in combination with mesenchymal stem cell treatment: a prospective study	wrong study design
Increased responsiveness to Toll-like receptor 4 stimulation in peripheral blood mononuclear cells from patients with recent onset rheumatoid arthritis	wrong study design
Intra-articular injection of culture-expanded adipose tissue-derived stem cells for knee osteoarthritis: Assessments with clinical symptoms and quantitative measurements of articular cartilage volume	wrong study design
Novel and targeted therapies for OA	wrong study design
Intra-articular infiltration of adipose-derived stromal vascular fraction cells slows the clinical progression of moderate-severe knee osteoarthritis: hypothesis on the regulatory role of intra-articular adipose tissue	wrong study design
Allogenic Human Umbilical Cord Blood-Derived Mesenchymal Stem Cells Are More Effective Than Bone Marrow Aspiration Concentrate for Cartilage Regeneration After High Tibial Osteotomy in Medial Unicompartmental Osteoarthritis of Knee	wrong study design
Cell type-specific dysregulation found to differentiate patient subsets of sjã– gren's disease	wrong study design
CCL20/CCR6 chemokine/receptor expression in bone tissue from osteoarthritis and rheumatoid arthritis patients: Different response of osteoblasts in the two groups	wrong study design
Cytokine release by human bone marrow stromal cells isolated from osteoarthritic and diabetic osteoarthritic patients in vitro	wrong study design

Bone Marrow Concentrate (BMC) Therapy in Musculoskeletal Disorders: Evidence-Based Policy Position Statement of American Society of Interventional Pain Physicians (ASIPP)	wrong study design
Biologic therapy in chronic pain management: a review of the clinical data and future investigations	wrong study design
Is Culture Expansion Necessary in Autologous Mesenchymal Stromal Cell Therapy to Obtain Superior Results in the Management of Knee Osteoarthritis?-Meta-Analysis of Randomized Controlled Trials	wrong study design
Human Amniotic Suspension Allograft Improves Pain and Function in Knee Osteoarthritis: A Prospective Not Randomized Clinical Pilot Study	wrong study design
The use of intra-articular injection of autologous micro-fragmented adipose tissue as pain treatment for ankle osteoarthritis: a prospective not randomized clinical study	wrong study design
Treatment of knee cartilage by cultured stem cells and three dimensional scaffold: a phase I/IIa clinical trial	wrong study design
Single- versus multiple-site harvesting techniques for bone marrow concentrate: Evaluation of aspirate quality and pain	wrong study design
Methods of Conservative Intra-Articular Treatment for Osteoarthritis of the Hip and Knee	wrong study design
Supplementation of articular cartilage-derived chondroprogenitors with bone morphogenic protein-9 enhances chondrogenesis without affecting hypertrophy	wrong study design
Microenvironmental and systematic evaluation of the immunome in osteoarthritis	wrong study design
Adipose-derived stem cells for treating knee osteoarthritis: relevant clinical trials and registration	wrong study design
Cartilage regeneration in osteoarthritic patients by a composite of allogeneic umbilical cord blood-derived mesenchymal stem cells and hyaluronate hydrogel: Results from a clinical trial for safety and proof-of-concept with 7 years of extended follow-up	wrong study design
No evidence for the use of stem cell therapy for tendon disorders: a systematic review	wrong study design
The present state of treatments for articular cartilage defects in the knee	wrong study design
Immunophenotyping of a stromal vascular fraction from microfragmented lipoaspirate used in osteoarthritis cartilage treatment and its lipoaspirate counterpart	wrong study design
Osteoarthritis year in review 2021: epidemiology & therapy	wrong study design
Prevention of Osteoarthritis and Future Strategies for Osteoarthritis Therapy - An Orthopaedic and Trauma-Surgical Perspective	wrong study design
New experimental strategies in cartilage surgery	wrong study design
Distinct degenerative phenotype of articular cartilage from knees with meniscus tear compared to knees with osteoarthritis	wrong study design

Evaluating the Current Literature on Treatments Containing Adipose-Derived Stem Cells for Osteoarthritis: a Progress Update	wrong study design
Current clinical evidence for the use of mesenchymal stem cells in articular cartilage repair	wrong study design
Outcomes at 2-Years Follow-Up After Hip Arthroscopy Combining Bone Marrow Concentrate	wrong study design
A prospective pilot study investigating the musculoskeletal pain in postmenopausal breast cancer patients receiving aromatase inhibitor therapy	wrong study design
Efficacy and safety of intra-articular therapies in rheumatic and musculoskeletal diseases: An overview of systematic reviews	wrong study design
Comparison of Bone Marrow Aspirate Concentrate and Allogenic Human Umbilical Cord Blood Derived Mesenchymal Stem Cell Implantation on Chondral Defect of Knee: Assessment of Clinical and Magnetic Resonance Imaging Outcomes at 2-Year Follow-Up	wrong study design
Persistence of B19 parvovirus in synovial membranes of patients with rheumatoid arthritis	wrong study design
Clinical and laboratory findings following transplantation of allogeneic adipose-derived mesenchymal stromal cells in knee osteoarthritis, a brief report	wrong study design
Autologous bone marrow concentrate: review and application of a novel intra-articular orthobiologic for cartilage disease	wrong study design
Biologic injections for osteoarthritis and articular cartilage damage: can we modify disease?	wrong study design
New treatments for osteoarthritis	wrong study design
Human decellularized bone scaffolds from aged donors show improved osteoinductive capacity compared to young donor bone	wrong study design
A role of synovial exosomes in osteoclast differentiation of inflammatory arthritis	wrong study design
Implantation of allogenic umbilical cord blood-derived mesenchymal stem cells improves knee osteoarthritis outcomes: Two-year follow-up	wrong study design
Intra-articular injection of autologous adipose-derived mesenchymal stem cells in the treatment of knee osteoarthritis	wrong study design
Cartilage Repair by Mesenchymal Stem Cell-Derived Exosomes: Preclinical and Clinical Trial Update and Perspectives	wrong study design
Mesenchymal stromal cell-derived extracellular matrix influences gene expression of chondrocytes	wrong study design
T cell proliferative response and antibody formation to citrullinated collagen type II in patients with rheumatoid arthritis	wrong study design
Mesenchymal Stem Cells for Treatment of Tendon and Ligament Injuries-clinical Evidence	wrong study design
A single step, centrifuge-free method to harvest bone marrow highly	wrong study design

concentrated in mesenchymal stem cells: results of a pilot trial	
An assessment of bone marrow mesenchymal stem cell and human articular cartilage derived chondroprogenitor cocultures vs. monocultures	wrong study design
Comparative analysis of fresh chondrocytes, cultured chondrocytes and chondroprogenitors derived from human articular cartilage	wrong study design
Mesenchymal stem cells - a promising strategy for treating knee osteoarthritis a meta-analysis	wrong study design
Which is the most effective one in knee osteoarthritis treatment from mesenchymal stem cells obtained from different sources?-A systematic review with conventional and network meta-analyses of randomized controlled trials	wrong study design
The effect of synthesized cartilage tissue from human adipose-derived mesenchymal stem cells in orthopedic spine surgery in patients with osteoarthritis	wrong study design
Cellular and Clinical Analyses of Autologous Bone Marrow Aspirate Injectate for Knee Osteoarthritis: A Pilot Study	wrong study design
Effect of intra-knee injection of autologous adipose stem cells or mesenchymal vascular components on short-term outcomes in patients with knee osteoarthritis: an updated meta-analysis of randomized controlled trials	wrong study design
Intra-articular injections of expanded mesenchymal stem cells with and without addition of platelet-rich plasma are safe and effective for knee osteoarthritis	wrong intervention
Clinical use of amniotic fluid in osteoarthritis: a source of cell therapy	wrong intervention
The efficacy of acupuncture combined with mesenchymal stem cell injection in the treatment of osteoarthritis of the knee	wrong intervention
Effect of Platelet-rich Plasma Injections on Cartilage T1rho in Knee Osteoarthritis	wrong intervention
BMAC in Severe Hip or Knee Osteoarthritis Awaiting Arthroplasty	wrong intervention
The Comparison of Knee Osteoarthritis Treatment With Bone Marrow Aspirate Concentrate, Leukocyte Rich Platelet Rich Plasma and Hyaluronic Acid	wrong intervention
Clinical results and second-look arthroscopic findings after treatment with adipose-derived stem cells for knee osteoarthritis	wrong intervention
Comparison between total knee arthroplasty and MCIC (autologous bone marrow mesenchymal-cell-induced-chondrogenesis) for the treatment of osteoarthritis of the knee	wrong intervention
Angiopoietin-like 3-derivative LNA043 for cartilage regeneration in osteoarthritis: a randomized phase 1 trial	wrong intervention
Biological Therapies for Knee Osteoarthritis. Intraosseous Injections of Platelet Rich Plasma Improve Pain, Function and Quality of Life as Compared to Intraarticular Injections: a Controlled, Double-Blind, Randomised Clinical Trial. Preliminary Results	wrong intervention

Autologous adipose tissue injection versus platelet-rich plasma (PRP) injection in the treatment of knee osteoarthritis: a randomized, controlled study - Study protocol	wrong intervention
A 24-month follow-up study of the effect of intra-articular injection of autologous microfragmented fat tissue on proteoglycan synthesis in patients with knee osteoarthritis	wrong intervention
Genicular nerve radiofrequency ablation for the treatment of avascular necrosis knee pain	wrong intervention
Enriched Peripheral Blood-Derived Mononuclear Cells for Treating Knee Osteoarthritis	wrong intervention
Growth factors in the treatment of early osteoarthritis	wrong intervention
Research trends of platelet-rich plasma therapy on knee osteoarthritis from 2011 to 2021: A review	wrong intervention
A phase I-II controlled randomized trial using a promising novel cell-free formulation for articular cartilage regeneration as treatment of severe osteoarthritis of the knee	wrong intervention
Patient-reported health outcomes for severe knee osteoarthritis after conservative treatment with an intra-articular cell-free formulation for articular cartilage regeneration combined with usual medical care vs. Usual medical care alone: A randomized controlled trial	wrong intervention
The recombinant Link module of human TSG-6 suppresses cartilage damage in models of osteoarthritis: A potential disease-modifying OA drug	wrong intervention
Do knee injection portals affect clinical results of bone marrow aspirate concentrate injection in the treatment of osteoarthritis? A prospective randomized controlled study	wrong intervention
Exploring the Involvement of NLRP3 and IL-1 Î^2 in Osteoarthritis of the Hand: Results from a Pilot Study	wrong intervention
Angiopoietin-like 3-derivative LNA043 for cartilage regeneration in osteoarthritis: a randomized phase 1 trial	wrong intervention
Allogenic Amniotic Tissue for Treatment of Knee and Hip Osteoarthritis	wrong intervention
Effect of elaeagnus angustifolia extract in bone tissue engineering nanofiber technology	wrong intervention
Early results of intra-articular micro-fragmented lipoaspirate treatment in patients with late stages knee osteoarthritis: A prospective study	wrong intervention
Role of platelet rich plasma injection grafts in osteoarthritis: a randomized controlled trial	wrong intervention
A prospective study to access the role of platelet rich plasma injection grafts in osteoarthritis: a randomized controlled trial	wrong intervention
DNA hypomethylation in inflammatory arthritis: reversal with methotrexate	wrong intervention
Evaluation of T-Cell Proliferation and Immunogenicity Assays with Genetically Engineered Chondrocytes, TissueGene-C	wrong intervention
Expression and Significance of MMPs in Synovial Fluid, Serum and PBMC	wrong intervention

Culture Supernatant Stimulated by LPS in Osteoarthritis Patients with or Without Diabetes	
Therapeutic effect of Î±-lipoic acid on osteoarthritis patients and its influence on TLR4/NF-ÎB and IL-23/IL-17 signaling pathway	wrong intervention
Cannabidiol for musculoskeletal regenerative medicine	wrong intervention
Nonsteroidal anti-inflammatory drug or glucosamine reduced pain and improved muscle strength with resistance training in a randomized controlled trial of knee osteoarthritis patients	wrong intervention
A Significant Increase in the Gene Expression of GATA-3 following the Treatment of Osteoarthritis Patients with Crocin	wrong intervention
Infrapatellar fat pad-derived mesenchymal stromal cell product for treatment of knee osteoarthritis: a first-in-human study with evaluation of the potency marker	no comparator
Autologous Adipose Tissue Derived Mesenchymal Stem Cells Therapy for Patients With Knee Osteoarthritis	no comparator
Clinical Trial of Allogenic Adipose Tissue-Derived Mesenchymal Progenitor Cells Therapy for Knee Osteoarthritis	no comparator
The effectiveness of knee osteoarthritis treatment by arthroscopic microfracture technique in combination with autologous bone marrow stem cells transplantation	no comparator
Cryopreserved Amniotic Suspension for the Treatment of Knee Osteoarthritis	no comparator
Allogeneic mesenchymal stromal cells in a cartilage clinical trial: stimulation of tissue regeneration without engraftment	no comparator
The influence of adipose-derived stromal vascular fraction cells on the treatment of knee osteoarthritis	no comparator
Final results of a phase I-II trial using ex vivo expanded autologous Mesenchymal Stromal Cells for the treatment of osteoarthritis of the knee confirming safety and suggesting cartilage regeneration	no comparator
Adipose mesenchymal stromal cell-based therapy for severe osteoarthritis of the knee: a phase I dose-escalation trial	no comparator
Development of Autologous Platelet-Rich Plasma Mixed-Microfat as an Advanced Therapy Medicinal Product for Intra-Articular Injection of Radio-Carpal Osteoarthritis: From Validation Data to Preliminary Clinical Results	no comparator
tissue engineering, embryonic, organ and other tissue specific stem cells: scaffold-free pellet-type autologous chondrocyte implantation (CARTILIFEÂ®) for for the restoration of articular cartilage defects: a randomized phase 2 clinical trial and extended 5-year clinical follow-up	no comparator
Mesenchymal stem cell injections improve symptoms of knee osteoarthritis	no comparator
MSC based therapy for severe osteoarthritis of the knee: The adipoa experience	no comparator
Intra articular injection of autologous bone marrow-derived mesenchymal stromal cells in patients with moderate to severe osteoarthritis	no comparator

Adipose-derived stem cells in patients with knee osetoarthritis: a randomised controlled trial evaluating pain, function and cartilage repair	no comparator
Intra-articular injections of expanded mesenchymal stem cells with and without addition of platelet-rich plasma are safe and effective for knee osteoarthritis	All groups stem cells
Intra-articular injection of mesenchymal stem cells for the treatment of osteoarthritis of the knee: A proof-of-concept clinical trial	All groups stem cells
Implantation of mesenchymal stem cells in combination with allogenic cartilage improves cartilage regeneration and clinical outcomes in patients with concomitant high tibial osteotomy	All groups stem cells
Value of multi-parameter magnetic resonance imaging of cartilage in evaluating efficacy of adipose derived mesenchymal progenitor cells on knee osteoarthritis	All groups stem cells
Human adipose-derived mesenchymal stem cells for osteoarthritis: a pilot study with long-term follow-up and repeated injections	All groups stem cells
Stem cells doses in knee osteoarthritis	All groups stem cells
Comparison of Clinical and Imaging Outcomes of Different Doses of Adipose-Derived Stromal Vascular Fraction Cell Treatment for Knee Osteoarthritis	All groups stem cells
Multi-compositional MRI evaluation of repair cartilage in knee osteoarthritis with treatment of allogeneic human adipose-derived mesenchymal progenitor cells	All groups stem cells
Mesenchymal Stem Cells in Knee Cartilage Injuries	All groups stem cells
Intra-articular injections of allogeneic human adipose-derived mesenchymal progenitor cells in patients with symptomatic bilateral knee osteoarthritis: a Phase I pilot study	All groups stem cells
Intra-articular Injection of Mesenchymal Stem Cells for the Treatment of Osteoarthritis of the Knee A 2-Year Follow-up Study	All groups stem cells
Multi-compositional MRI evaluation of repair cartilage in knee osteoarthritis with treatment of allogeneic human adipose-derived mesenchymal progenitor cells	All groups stem cells
Intra-articular fat derived stem cell injections effect on pain, stiffness and function in osteoarthritis	All groups stem cells
Real-world evidence of mesenchymal stem cell therapy in knee osteoarthritis: a large prospective two-year case series	All groups stem cells
Effect of autologous adipose-derived mesenchymal stem cell therapy in the treatment of an osteochondral lesion of the ankle	All groups stem cells
Effect of autologous adipose-derived mesenchymal stem cell therapy in the treatment of acromioclavicular joint osteoarthritis	All groups stem cells
The effect of autologous adipose derived mesenchymal stem cell therapy in the treatment of a large osteochondral defect of the knee following unsuccessful surgical intervention of osteochondritis dissecans - a case study	All groups stem cells
Clinical and Radiological Comparison of Single and Double Intra-articular Injection of Adipose-Derived Stromal Vascular Fraction for Knee	All groups stem cells

Osteoarthritis	
The Efficacy Of Acupuncture Combined With Mesenchymal Stem Cell Injection In The Treatment Of Osteoarthritis Of The Knee	All groups stem cells
Biological injection therapy with leukocyte-poor platelet-rich plasma induces cellular alterations, enhancement of lubricin, and inflammatory downregulation in vivo in human knees: A controlled, prospective human clinical trial based on mass spectrometry imaging analysis	wrong outcome
Cost Effectiveness of Allogeneic Umbilical Cord Blood-Derived Mesenchymal Stem Cells in Patients with Knee Osteoarthritis	wrong outcome
Gene expression and functional comparison between multipotential stromal cells from lateral and medial condyles of knee osteoarthritis patients	wrong outcome
New clinical treatments	wrong outcome
Effects of Conditioned Medium From Osteoarthritic Cartilage Fragments on Donor-Matched Infrapatellar Fat Pad-Derived Mesenchymal Stromal Cells	wrong outcome
Adipose mesenchymal stromal cells determine the switching of the pro-inflammatory profile of synovial osteoarthritic macrophages	wrong outcome
Bone marrow-derived cell mobilization by G-CSF to enhance osseointegration of bone substitute in high tibial osteotomy	wrong outcome
Synovial Mesenchymal Stem Cells Derived From the Cotyloid Fossa Synovium Have Higher Self-renewal and Differentiation Potential Than Those From the Paralabral Synovium in the Hip Joint	wrong outcome
Local administered adipose-derived mesenchymal stromal cells reduce experimental oa-pathology via interleukin- 1Î²-mediated immunomodulation of pro-inflammatory PMNS	wrong outcome
Differences in surface marker expression and chondrogenic potential among various tissue-derived mesenchymal cells from elderly patients with osteoarthritis	wrong outcome
Comparing the allogeneic inflammatory reaction between mesenchymal-lineage cells derived from different origins	wrong outcome
The expression and function of metastases associated lung adenocarcinoma transcript-1 long non-coding RNA in subchondral bone and osteoblasts in osteoarthritis patients	wrong intervention

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2. AVASCULAR NECROSIS OF HIP

i. **Key question in PICO format**

ii. **Search strategy**

iii. **PRISMA flow diagram**

iv. **Summary of included studies**

v. **Classification of studies based on level of stem cell manipulation**

vi. **Evidence to decision framework**

vii. **Data extraction**

viii. **List of excluded studies**

i. Key question in PICO format:

Population: Patients with avascular necrosis
Intervention: Any Stem cell and product derived from stem cells
Comparator: Usual Care/ Conventional Care
Critical Outcomes: Efficacy: Reduction in pain, Disability; Safety: Severe Adverse Events

ii. Search Strategy (September 2023):

PubMed Search

Concept	Query Key Words	Results
Population	"Avascular Necrosis" OR "aseptic necrosis" OR "Femoral head necrosis" OR "Femoral head avascular necrosis" OR osteonecrosis (70) OR "Femur head necrosis" {MeSH Terms} OR "Avascular Necrosis" OR "Avascular necrosis of femoral head" OR "Hip"	33207
Intervention	"Stem Cell Therapy" OR "Cell and tissue-based therapy" MesH terms} OR "Biological Therapy" [MeSH terms} OR "Biological therapy" OR "Progenitor Cell" OR "Regenerative medicine" OR "Regenerative therapy" OR "Cellular therapy" OR BMSC OR PBMSC OR UCMSC OR ACMSC OR "Peripheral blood mononuclear cells" OR "Bone marrow Mononuclear cells" OR "umbilical cord-derived mesenchymal stem cells" OR "Amniotic fluid-derived stem cells"	930685
Search Strategy	("Avascular osteonecrosis"[ALL Fields] OR ("aseptic osteonecrosis"[All Fields] OR "Femoral head"[All Fields] OR "Femoral head necrosis"[All Fields] OR "Femoral head avascular necrosis"[All Fields] OR ("Osteonecrosis"[MeSH Terms] OR "Femur head necrosis"[MeSH Terms] OR "Avascular Necrosis"[All Field] OR "Avascular necrosis of femoral head"[All Fields] OR "Aseptic necrosis of femoral head"[All Fields])))) AND ("Stem cell therapy"[All Fields] OR ("Cell and tissue based therapy"[MeSH Terms] OR "Biological Therapy"[MeSH Terms] OR "Biological therapies"[All Fields] OR "Progenitor cell"[All Fields] OR "Regenerative medicine"[All Fields] OR "Regenerative Therapy"[All Fields] OR "Cellular Therapy"[All Fields] OR "BMSC"[All Fields] OR9"pbmsc"[All Fields] OR "pbmscs"[All Fields]) OR ("ucmsc'[All Fields] OR "ucmscs"[All Fields] OR "ACMSC"[All Fields] OR "Peipheral blood mononuclear cells"[All Fields] OR "Bone marrow Mononuclear cells"[All fields] OR "umblical cord derived mesenchymal stem cells"[All Fields] OR Amniotic fluid-derived stem cells"[All Fields]))	2088

Embase Search:

Concept	Query Key Words	Results
Population	"Avascular necrosis" OR "aseptic necrosis" OR" femoral head" OR "femoral head necrosis" OR "femoral head avascular necrosis" OR "aseptic necrosis of femoral head"	44117
Intervention	"Cell and tissue-based therapy" OR "Biological Therapy" OR "biological therapies" OR "stem cell" OR "regenerative therapy" OR "regenerative medicine" OR "pbmsc" OR "ucmsc" OR "bmsc" OR "acmsc" OR "peripheral blood mononuclear cell" OR "bone marrow-derived mononuclear cell" OR "umbilical cord mesenchymal stem cell"	903310
Search Strategy	"Avascular necrosis" OR "aseptic necrosis" OR" femoral head" OR "femoral head necrosis" OR "femoral head avascular necrosis" OR "aseptic necrosis of femoral head" AND "cell and tissue-based therapy" OR "Biological Therapy" OR "biological therapies" OR "stem cell" OR "regenerative therapy" OR "regenerative medicine" OR "pbmsc" OR "ucmsc" OR "bmsc" OR "acmsc" OR "peripheral blood mononuclear cell" OR "bone marrow-derived mononuclear cell" OR "umbilical cord mesenchymal stem cell"	1627

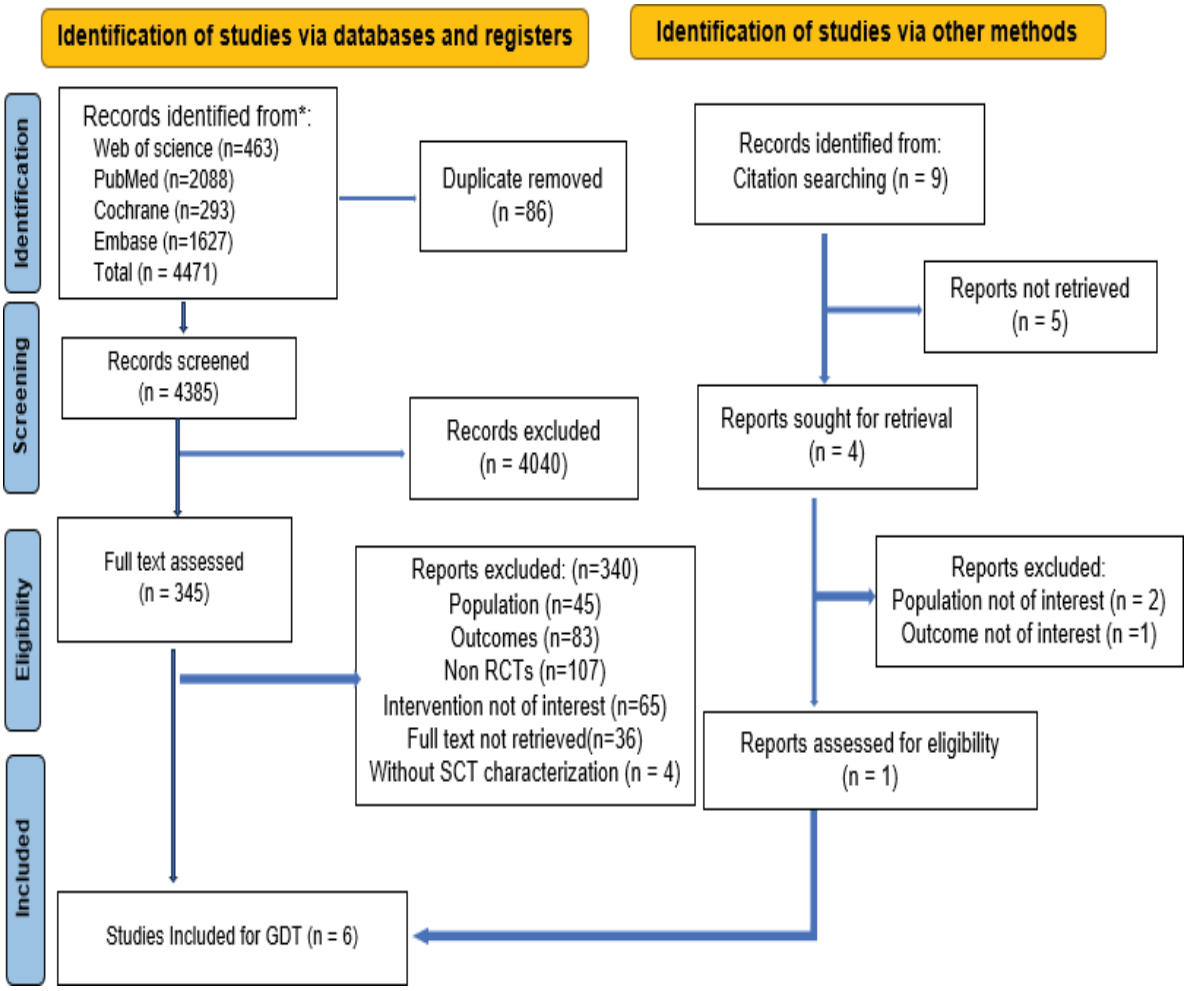
Cochrane Search:

Concept	Query-Keywords	Results
Population	MeSH descriptor: [Femur Head] explode all trees Femur head NEXT Avascular Necrosis" OR "aseptic necrosis" OR "Femoral head necrosis" OR "Femoral head avascular necrosis" OR osteonecrosis OR "Femur head necros" OR "Avascular Necrosis" OR "Avascular necrosis of femoral head	337
Intervention	MeSH descriptor: [Stem Cells] explode all trees Regenerative therapy OR Cell therapy OR"Stem Cell Therapy" OR "Cell and tissue-based therapy"{MesH terms OR "Biological Therapy" OR "Biological therapy" OR "Progenitor Cell" OR "Regenerative medicine" OR "Regenerative therapy" OR "Cellular therapy" OR BMSC OR PBMSC OR UCMSC OR ACMSC OR "Peripheral blood mononuclear cells" OR "Bone marrow Mononuclear cells" OR "umbilical cord-derived mesenchymal stem cells" OR "Amniotic fluid-derived stem cells	162266
Search strategy	AND MeSH descriptor: [Stem Cells] explode all trees Regenerative therapy OR Cell therapy OR"Stem Cell Therapy" OR "Cell and tissue-based therapy"{MesH terms} OR "Biological Therapy" OR "Biological therapy" OR "Progenitor Cell" OR "Regenerative medicine" OR "Regenerative therapy" OR "Cellular therapy" OR BMSC OR PBMSC OR UCMSC OR ACMSC OR "Peripheral blood mononuclear cells" OR "Bone marrow Mononuclear cells" OR "umbilical cord-derived mesenchymal stem cells" OR "Amniotic fluid-derived stem cells	293

Web of Science Search:

Concept	Query-Keywords	Results
Population	ALL=(Avascular Necrosis" OR "aseptic necrosis" OR "Femoral head necrosis" OR "Femoral head avascular necrosis" OR osteonecrosis OR "Femur head necrosis" OR "Avascular Necrosis" OR "Avascular necrosis of femoral head")	225
Intervention	ALL=("Stem Cell Therapy" OR "Cell and tissue-based therapy" OR "Biological Therapy" OR "Biological Therapy" OR "Progenitor Cell" OR "Regenerative medicine" OR "Regenerative therapy" OR "Cellular therapy" OR BMSC OR PBMSC OR UCMSC OR ACMSC OR "Peripheral blood mononuclear cells" OR "Bone marrow Mononuclear cells" OR "umbilical cord-derived mesenchymal stem cells" OR "Amniotic fluid-derived stem cells)	1226723
Search strategy	ALL=(Avascular Necrosis" OR "aseptic necrosis" OR "Femoral head necrosis" OR "Femoral head avascular necrosis" OR osteonecrosis OR "Femur head necrosis" OR "Avascular Necrosis" OR "Avascular necrosis of femoral head") OR ALL=("Stem Cell Therapy" OR "Cell and tissue-based therapy" OR "Biological Therapy" OR "Biological Therapy" OR "Progenitor Cell" OR "Regenerative medicine" OR "Regenerative therapy" OR "Cellular therapy" OR BMSC OR PBMSC OR UCMSC OR ACMSC OR "Peripheral blood mononuclear cells" OR "Bone marrow Mononuclear cells" OR "umbilical cord-derived mesenchymal stem cells" OR "Amniotic fluid-derived stem cells)	463

iii. PRISMA Flow Diagram:



iv. Summary of included studies:

Study	Population	Intervention	Comparison	Outcomes	Comments
Zhao et al. 2012[1]	ONFH	BMMSC+CD	CD	THR, HHS	Included
Sen et al. 2012[2]	ONFH	BMNSC+CD	CD	HHS	Included
Mao et al. 2015[3]	ONFH	PBSC+G-CSF + CD	CD	THR, HHS	Included
Pepke et al. 2016[4]	ONFH	BMASC+CD	CD	THR, HHS	Included
Hauzeur et al. 2017[5]	ONFH	BMASC+CD	CD + Saline injection	THR, VAS, WOMAC	Included
Jayankura et al. 2023[6]	ONFH	BMMSC+CD	CD+ placebo	THR, WOMAC	Included
Tabatabae et al. 2015[7]	Early-Stage ONFH	MNC	CD	WOMAC, VAS, MRI score, THR	Stem cell is not characterized (Mononuclear cells)
Li et al. 2020[8]	ONFH	CD+BBC	CD	WOMAC, VAS, DP, THR	Stem cell is not characterized (Bone marrow buffy coat)
Li et al. 2021[9]	ONFH	ACD, BBC, and ABR grafting	ACD, β-TCP, and ABR grafting	HHS, THR, Survival	Stem cell is not characterized (Bone marrow buffy coat)
Ma et al. 2014[10]	ONFH	CD+BBC	CD+ABMC	Lequesne Index, WOMAC, VAS, Disease Progression, THR	Stem cell is not characterized (Bone marrow buffy coat)

v. Classification of studies on the basis of level of manipulation of the stem cell/ Stem cell derived product used (*interpreted by the Secretariat as defined by CDSCO* and the information provided in the trial itself*):

S. No.	Trial Details	Intervention	Level of manipulation	Information extracted from trial
1.	Zhao et al. 2012	ABMSC	More	*"BM derived BMMSCs were subjected to proliferation in vitro for two weeks, after which about 2×10⁶ BMMSCs were harvested and prepared in 2 ml normal saline solution and later injected into the osteo-necrotic site in the femoral head with a puncture needle through the bored plug and the ecompression tunnel."*
2.	Pepke et al. 2016	Bone marrow aspirate concentrate	Less	*"Bone marrow volume harvested was 200 to 220 ml. 12 ml of BM concentrate suspension was isolated. 2 ml of the final cell concentrate volume were collected, 10 mL of BMAC was instilled into the necrotic zone.."*

3.	Sen et al. 2012	BMNC (bone marrow mononuclear cell) concentrate	Less	*"The aspirate was processed in the laboratory (by Ficoll interface separator) until the mononuclear cell concentrate (MNC, 2mL) was available. This took approximately 2 hours. Part of the aspirate was subjected to immunophenotypíng, cell viability, and microbiological assays for quality control. As a part of the protocol, final cell suspension was checked for MNC count, CD34+count (active stem cells), and the cellular viability. The total counts were maintained approximately 5×10^{8} MNC to keep the CD34+ cell count more than 5×10^{7}."*
4.	Mao et al. 2015	PBSCs	Less	*"Before cell infusion, PBSCs were harvested from the patients by apheresis technique using a COBESpectra Apheresis System (COBE BCT Inc., Lakewood, CO, USA) after subcutaneous injections of G-CSF at a dosage of 10mg/kg for 4 days to mobilize the PBSCs (Supporting Fig. S2). The collection process was carried out according to the mononuclear cell collection method, which was recommended in the COBE Spectra Apheresis System operator's manual provided by the manufacturer. (42) The number of CD34+ cells in the cell suspension was calculated. Then, the PBSCs were infused into the femoral head as described."*
5.	Hauzeur et al. 2017	BMAC	Less	*"The BMAC had a final volume of 48.33±1.16ml. The mean number of nucleated cells injected was $3.46 \pm 0.36 \times 10^{9}$ including 1.5 ± 0.28% CD34+."*
6.	Jayankura et al. 2023	Autologous osteoblastic cells	More	*"Mononuclear cells were isolated from bone marrow using density (FicollTM) gradient centrifugation. The cells were then plated and cultured ex vivo in a culture medium containing specific growth factors triggering differentiation to ward osteoblastic lineage under strictly controlled conditions and according to good manufacturing practice guidelines."*

* as defined by CDSCO in Annexure- I of the guideline document

vi. Evidence to Decision Framework:

QUESTION

What is the efficacy and safety of Stem Cell Therapy vs Standard of Care/Usual care in patients with Avascular Necrosis?	
POPULATION:	Avascular Necrosis of Hip
INTERVENTION:	Stem Cell Therapy
COMPARISON:	Standard of Care/ Usual Care

MAIN OUTCOMES:	Reduction in pain and disability, and improvement in function- Harris Hip Score, VAS Score; WOMAC Score; Serious Adverse Events
SETTING:	Hospital/Tertiary Care setting
PERSPECTIVE:	Population
BACKGROUND:	Avascular necrosis (AVN) is a debilitating condition marked by the death of bone tissues with no effective therapies to slow down its progression. The hip joint is the most commonly affected joint, accounting for two-third of cases and is commonly known as osteonecrosis of the femoral head (ONFH). Symptomatic ONFH has a high risk of progression to femoral head collapse (FHC) leading to total hip replacement (THR) as last resort of treatment.
CONFLICT OF INTERESTS:	None

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○No ○Probably no ○Probably yes ●Yes ○Varies ○Don't know	Osteonecrosis of femoral head is a disabling condition of young individuals with ill-defined etiology and pathogenesis. Remains untreated, about 70–80% of the patients progress to secondary hip arthritis. Both operative and nonoperative treatments have been described with variable success rate. Early diagnosis and treatment is the key for success in preserving the hip joint. Once femoral head collapses (>2 mm) or if there is secondary degeneration, hip conservation procedures become ineffective and arthroplasty remains the only better option.[11]	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	**Harris Hip Score:** Evidence from four trials, with a total of 262 participants reporting the Harris Hip score showed a mean difference of 4.09 (95% CI: -4.08 to 12.26) in the stem cell transplantation arm in comparison to usual care at the end of follow up which ranged from 24 to 36 months. The difference was statistically non-significant. **VAS:** Evidence from two trials, with a total of 71 participants, reporting the VAS showed a mean difference of -0.50 (95% CI: -0.74 to -0.27) in the stem cell transplantation arm compared to those on usual care at the end of 24 months. There seems to be a decrease in pain as the difference was statistically significant. However, it was less than half of MCID of 2. Therefore, the reduction in pain is unimportant clinically. **WOMAC:** Evidence from one trial with a total of 54 participants reporting the WOMAC score showed a mean difference of -9.2 (95% CI -24.43 to 6.03) in the stem cell group in comparison to usual care, which was statistically non-significant. Evidence from one trial with a total of 46 participants reporting the WOMAC score using subscales A and B showed a difference of -0.90 (95% CI: -3.53 to 1.73) and -1.40 (95% CI: -4.03 to 1.23) in the stem cell group in comparison to usual care at the end of follow- up respectively. The result was statistically non-significant. **Total Hip Replacement:** Evidence from five trials with 311 participants showed no statistically significant increase in the number of participants requiring total hip replacement after stem cell therapy as compared to usual care at the end of 24 months (RR 1.05 (95% CI 0.73 to 1.51)).	The GDG decided a cut-off of 20% for the MCID.
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	None of the trials reported any serious adverse events. The evidence is insufficient to draw firm conclusions due to limited long term follow up of trials.	
Certainty of evidence		

What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The evidence in this review is of very low quality due to high risk of bias, inconsistency and imprecision in the effect shown by stem cell therapy.	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	Main outcome is clinical improvement in the form of reduced pain and increased functional activity which is likely to be highly valued by most persons.[12]	
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○Favors the comparison ○Probably favors the comparison ●Does not favor either the intervention or the comparison ○Probably favors the intervention ○Favors the intervention ○Varies ○Don't know	It is less clear if benefits of stem cell intervention outweigh the harms due to small to trivial benefit, based on limited evidence.	
Resources required How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
●Large costs ○Moderate costs ○Negligible costs and savings ○Moderate savings ○Large savings ○Varies ○Don't know	No direct evidence of the resources required in stem cell transplantation in patients with avascular necrosis was identified.	
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○Very low ○Low ●Moderate ○High ○No included studies	No research evidence was identified.	The GDG members were fairly certain that stem cell therapy requires large resources.
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○Favors the comparison ●Probably favors the comparison ○Does not favor either the intervention or the comparison ○Probably favors the intervention ○Favors the intervention ○Varies ○No included studies	No direct research evidence was identified.	The intervention was not found to be effective and hence the committee deferred to comment on cost effectiveness.
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○Reduced ●Probably reduced ○Probably no impact ○Probably increased	No research evidence was identified.	As stem cell therapy is an expensive treatment offered only at tertiary care centers, it is likely to

○Increased ○Varies ○Don't know		increase inequity as it would not be affordable by all.
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○No ○Probably no ●Probably yes ○Yes ○Varies ○Don't know	Despite uncertainty regarding the medical risks and benefits associated with stem cell injections, patients with avascular necrosis have very high expectations from stem cell therapy.[13]	
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○No ○Probably no ●Probably yes ○Yes ○Varies ○Don't know	No research evidence was identified.	Stem Cell transplantation can be performed only in tertiary care centers so feasibility in lesser equipped hospitals and clinics is not possible.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	**Moderate**	High			No included studies
COST EFFECTIVENESS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Use only in the context of rigorously conducted RCTs	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	●	○	○	○

CONCLUSIONS

Recommendation

Stem Cell Therapy is **not recommended** in routine practice for the treatment of avascular necrosis of hip. It may be used only in the context of rigorously conducted randomized controlled trials.

Justification

This recommendation has been made as there is very low certainty evidence of trivial reduction in pain and no improvement in function. There is little or no difference in undesirable effects between stem cell therapy and usual care. In addition, the follow up period is limited to comment on the long-term safety of stem cell therapy. Results should be interpreted with caution, in view of various study limitations like high risk of bias, small number of participants and/or events.

vii. Data Extraction:

Data Extraction Method:

The independent data extraction and screening procedure was carried out by two authors. Any disagreements were sorted out with the help of a third author. According to pre-established eligibility criteria, the titles and abstracts of the retrieved citations were first assessed in the screening process. Following that, we thoroughly examined the complete text of the potentially relevant citations for appropriateness. All the required study data, including variables like first author, publication year, country, number of participants and their demographics, number of hips and stage of AVN (ARCO staging), SCT and comparison intervention details (source and counts of SCT), follow-up, adverse events, THR, and any other pertinent information from the included studies were extracted using a standardized Excel sheet. Two authors independently evaluated the methodological quality of each eligible trial according to the criteria provided by Cochrane's Risk of Bias 2 tool.

Data Extraction Sheet:

Study 1, Title	Treatment of early-stage osteonecrosis of the femoral head with autologous implantation of bone marrow-derived and cultured mesenchymal stem cells
Author Year	Zhao et al. 2012[1]
Study type:	RCT
Number of participants:	93
Countries and setting:	China
Duration of study Follow up (post intervention):	5
Method of assessment of disease condition:	THR and HHS
Subgroup analysis within study:	ARCO stage patients with stage groups IC, IIC, IIB, IIC
Inclusion criteria:	Patients age between 18 and 55 years, presence of osteonecrosis stages from IC to IIC according to the Association Research Circulation Osseous (ARCO) classification and risk factors, such as trauma, corticosteroid use, alcohol abuse, Caisson disease, and other idiopathic mechanisms
Exclusion criteria:	Pregnancy, current and previous infections, skeletal immaturity, immunosuppressive drug therapy, a history of inflammatory arthritis, cardiovascular diseases, prior systemic corticosteroid treatment, and mental health problems.

Recruitment/selection of patients:	This single-center randomized clinical trial was conducted in a university-affiliated hospital in China between May 2004 and July 2006. Written informed consent was obtained from each patient before enrollment. Patients were randomly divided into two groups following the randomization sequence created by a third party not involved in this study at the time of patient admission. Patients in one group were treated with core decompression and patients in the other group were treated with femoral head autologous implantation of cultured BMMSCs.
Intervention: Type of stem cells with method of characterization, Route of administration, Dose	ABMSC, BM derived BMMSCs were subjected to proliferation in vitro for two weeks, after which about 2×10^6 BMMSCs were harvested and prepared in 2 ml normal saline solution and later injected into the osteo-necrotic site in the femoral head with a puncture needle through the bored plug and the decompression tunnel.
Outcomes reported with time points	THR (12, 24, 36, 48, 60) months, HHS (12, 24, 36, 48, 60) months
Funding	Supported by China National Natural Science Foundation grants 30670542 and 30471752 (to D. Zhao)
RoB2 Assessment: Specify separately for each domain	Randomization process: Low risk Deviation from intended interventions: High risk Missing outcome data: High risk Measurement of the outcome: Low risk Selection of reported result: Low risk

Study 2, Title	Early Results of Core Decompression and Autologous Bone Marrow Mononuclear Cells Instillation in Femoral Head Osteonecrosis: A Randomized Control Study
Author Year	Sen et al. 2012[2]
Study type:	RCT
Number of participants:	40
Countries and setting:	India
Duration of study Follow up (post intervention):	2
Method of assessment of disease condition:	Harris Hip score, X-ray, and magnetic resonance imaging (MRI)

Subgroup analysis within study:	NR
Inclusion criteria:	NR
Exclusion criteria:	NR
Recruitment/selection of patients:	Patients were enrolled after obtaining their informed consent. The hips were divided randomly into 2 treatments groups. patients in group A with 25 hips (18males and 7 females, 16 nontraumatic osteonecrosis and 9 traumatic osteonecrosis) were treated with CD alone, whereas those in group B (26 hips, 19males and 7 females, 18 nontraumatic osteonecrosis and 8 traumatic osteonecrosis) were treated with CD with simultaneous instillation of marrow-derived mononuclear cells (BMMNC or stem cell) into the core tract. Both groups of patients were operated on by the same surgeon.
Intervention: Type of stem cells with method of characterization, Route of administration, Dose	BMNSC, 120 to 180 mL of BM was aspirated from the posterior iliac crest with 10mL syringe, processed in the laboratory for 2 hours (by Ficoll interface separator) until the mononuclear cell concentrate (MNC, 2 mL), The total counts were maintained at 5×10^8 MNC to keep the $CD34^+$ cell count more than 5×10^7. Under the anesthesia, the BMNC concentrate was instilled into the predrilled tracts
Outcomes reported with time points	HHS (12, 24) months
Funding	NR
RoB2 Assessment: Specify separately for each domain	Randomization process: High risk Deviation from intended interventions: Low risk Missing outcome data: Low risk Measurement of the outcome: High risk Selection of reported result: Low risk

Study 3, Title	Combination Treatment of Biomechanical Support and Targeted Intra-arterial Infusion of Peripheral Blood Stem Cells Mobilized by Granulocyte-Colony Stimulating Factor for the Osteonecrosis of the Femoral Head: A Randomized Controlled Clinical Trial
Author Year	Mao et al. 2014[3]
Study type:	RCT
Number of participants:	55
Countries and setting:	China

Duration of study Follow up (post intervention):	3
Method of assessment of disease condition:	Harris Hip score to measure the hip function., x-ray, and conversion to THR was designed as the endpoint to evaluate the efficacy of the treatment
Subgroup analysis within study:	ARCO stage patients with stage groups I, II, IIIA
Inclusion criteria:	Patients were aged 18 to 65 years and had ONFH stages Ito IIIA in compliance with the Association Research Circulation Osseous (ARCO) classification.
Exclusion criteria:	Current or previous inflammatory arthritis or other disease of hip joint, skeletal immaturity, serious cardiovascular disease, hepatic or renal disease, a history of hip joint surgery, still on corticosteroid therapy, pregnant or lactating women, malignant disease, serious current infection or haematological disease, and mental health disorders.
Recruitment/selection of patients:	Patients were enrolled after obtaining their informed consent. The hips were divided randomly into 2 treatments groups. patients in group A with 25 hips (18males and 7 females, 16 nontraumatic osteonecrosis and 9 traumatic osteonecrosis) were treated with CD alone, whereas those in group B (26 hips, 19males and 7 females, 18 nontraumatic osteonecrosis and 8 traumatic osteonecrosis) were treated with CD with simultaneous instillation of marrow-derived mononuclear cells (BMMNC or stem cell) into the core tract. Both groups of patients were operated on by the same surgeon.
Intervention: Type of stem cells with method of characterization, Route of administration, Dose	PBSC+G-CSF, A 50 mL heparinized syringe was connected to the BM aspiration needle and used to harvest the BM (superior posterior iliac spine), BM was centrifuged at 1500 rpm/10 minutes, BBC from the interface containing enriched BM cells was collected & loaded onto the porous cylindrical bone drop by drop, the average BM cells loaded to bone were approximately 3×10^9 nucleated cells. The BBC was seeded on the cylindrical bone for 2 minutes before implantation. The bone graft was inserted into the necrotic region through the trephine. PBSCs were harvested by apheresis technique after subcutaneous injections of G-CSF at a dosage of 10 mg/kg for 4 days to mobilize the PBSCs, and were infused into the femoral head.
Outcomes reported with time points	HHS (3, 6, 12, 18, 24, 30, 36) months
Funding	NR
RoB2 Assessment: Specify separately for each domain	Randomization process: Low risk Deviation from intended interventions: Low risk Missing outcome data: Low risk

	Measurement of the outcome: Low risk Selection of reported result: Low risk

Study 4, Title	Core decompression and autologous bone marrow concentrate for treatment of femoral head osteonecrosis: A randomized prospective study
Author Year	Pepke et al. 2016[4]
Study type:	RCT
Number of participants:	24
Countries and setting:	Germany
Duration of study Follow up (post intervention):	2
Method of assessment of disease condition:	For clinical outcome the VAS and HHS were measured. For radiological outcome the volume of the necrotic zone
Subgroup analysis within study:	NR
Inclusion criteria:	Age over 18 years and the presence of stage II femoral head osteonecrosis according to the Association of Research Circulation Osseous (ARCO) classification.
Exclusion criteria:	NR
Recruitment/selection of patients:	All patients signed the informed consent, the institutional review board of the hospital approved the study; all procedures were performed in accordance with the Declaration of Helsinki.
Intervention: Type of stem cells with method of characterization, Route of administration, Dose	BMASC, Bone marrow volume harvested was 200 to 220 ml. 12 ml of BM concentrate suspension was isolated. 2 ml of the final cell concentrate volume (BMAC) were collected, 10 mL of BMAC was instilled into the necrotic zone through the canulated trephine drill after removal of the central k- wire. Per donor, 2×10^6 mononucleated cells (MNC) out of the native BM and the BMAC were seeded into three T25 tissue culture flasks each and cultured in standard medium. After seven days of culturing, cells were washed with phosphate-buffered saline (PBS), and fixed with 70% ethanol stained with toluidin blue.
Outcomes reported with time points	HHS and THR at (12 and 24) months
Funding	NR
RoB2 Assessment: Specify	Randomization process: High risk

separately for each domain	Deviation from intended interventions: Low risk Missing outcome data: Low risk Measurement of the outcome: Some concerns Selection of reported result: Low risk

Study 5, Title	Inefficacy of autologous bone marrow concentrate in stage three osteonecrosis: a randomized controlled double-blind trial
Author Year	Hauzeur et al. 2017[5]
Study type:	RCT
Number of participants:	38
Countries and setting:	Belgium
Duration of study Follow up (post intervention):	2
Method of assessment of disease condition:	For clinical outcome the THR, VAS and WOMAC were measured.
Subgroup analysis within study:	WOMAC subgroup (WOMAC A score and WOMAC B score)
Inclusion criteria:	Patients aged 18 years or older suffering from ARCO stage 3 non-traumatic ONFH with a surface collapse lower than 30% of the entire articular surface together with a dome depression of no more than 4 mm, and who had signed the written consent form.
Exclusion criteria:	Evidence of malignant disorder in the past five years, contraindication to undergo an MRI, or a positive Serological test for HIV, hepatitis B or hepatitis C.
Recruitment/selection of patients:	A centralized assignment to treatment groups was performed for the two centres. The subject under investigation was patient's hip. We therefore randomly allocated hips to a core decompression procedure associated with BMAC implantation (BMAC group) or saline implantation.
Intervention: Type of stem cells with method of characterization, Route of administration, Dose	BMASC, 400 mL of BM was harvested from the posterior iliac crests and concentrated to a final volume of 50 ml. 4 mm trephine was inserted through the great trochanter, the neck, and the femoral head in the necrotic lesion. BM is aspirated with 10mL syringes rinsed with a buffer solution containing 400 mL of phosphate-buffered saline solution, transferred into the bag of the bone- marrow-collection kit (R4R 2107; Baxter, Deerfield, Illinois) to obtain a final volume of 400 mL of bone marrow. Fibroblast CFU were used as an indicator of stromal cell activity. The mean number of

	fibroblasts CFU was 92 ± 9/10^7cells. The sorted bone marrow-mononuclear cells contained lymphocytoid cells (mean, 29% ± 2.2%), monocytoid cells (4%±1%), and myeloid cells (6%±1.3%). Injection of the BM The 50 mL of mononuclear cells is then injected through the trephine that was placed into the necrotic lesion.
Outcomes reported with time points	WOMAC and THR at 24 months
Funding	Fund for Scientific Research of Belgium (FNRS)and the hospitals communities, University hospital of Liège and the Erasme hospital.
RoB2 Assessment: Specify separately for each domain	Randomization process: Low risk Deviation from intended interventions: Low risk Missing outcome data: High risk Measurement of the outcome: Low risk Selection of reported result: Low risk

Study 6, Title	Does Adjunction of Autologous Osteoblastic Cells Improve the Results of Core Decompression in Early-stage Femoral Head Osteonecrosis? A Double-blind, Randomized Trial
Author Year	Jayankura et al. 2023[6]
Study type:	RCT
Number of participants:	64
Countries and setting:	Belgium, Netherlands, France, Germany, UK
Duration of study Follow up (post intervention):	2
Method of assessment of disease condition:	For clinical outcome the THR and WOMAC were measured
Subgroup analysis within study:	NR
Inclusion criteria:	Men or women aged 18 to 70 years with a diagnosis of nontraumatic ONFH and ARCO Stages I or II (no fracture of the necrotic femoral head) ONFH on radiographs and MRI.
Exclusion criteria:	presence of ARCO Stage ≥ III ONFH of patients
Recruitment/selection of	Patients were randomized (1:1) to the treatment groups, and stratification according to ARCO stage.

patients:	The study was conducted in a double-blind manner. Bone marrow harvesting or sham intervention was conducted by an independent physician in each institution who was not otherwise involved in any other study-related procedures; all other investigators and patients were blind to treatment assignment.
Intervention: Type of stem cells with method of characterization, Route of administration, Dose	BMMSC, BM (between 30 and 50 mL) was harvested from the patient's hip (iliac crest). Mononuclear cells were isolated from bone marrow using density (FicollTM) gradient centrifugation. The cells were then plated and cultured ex vivo in a culture medium containing specific growth factors triggering differentiation toward osteoblastic lineage under strictly controlled conditions. 3 weeks after cell harvesting, osteoblastic cells were provided to the surgeon in prefilled, single dose, ready-to-use syringes containing cell suspension ($20x10^6$cells) in 5mLof phosphate-buffered saline and human serum albumin (20%). Using trephine, the surgeon implanted the patients with a single 5 mL dose of either the osteoblastic cell suspension or placebo in the necrotic lesion.
Outcomes reported with time points	WOMAC (at 1, 3, 6, 12 months) and THR (at 1, 3, 6, 12, 18, 24, 36 and 48 months)
Funding	NR
RoB2 Assessment: Specify separately for each domain	Randomization process: High risk Deviation from intended interventions: Low risk Missing outcome data: High risk Measurement of the outcome: Low risk Selection of reported result: Low risk

viii. List of excluded studies:

S. No.	Study	Year	Title	Reference	Reason of Exclusion
1	Rastogi et al.	2013	Intralesional autologous mesenchymal stem cells in management of osteonecrosis of femur: a preliminary study.	Musculoskeletal surgery 2013. 97,3: 223-8	Study design (Active comparator, both groups had stem cells as intervention)
2	Hauzeur et al.	2020	Did Osteoblastic Cell Therapy Improve the Prognosis of Pre-fracture Osteonecrosis of the Femoral Head? A Randomized, Controlled Trial	Clinical orthopaedics and related research 2020. 478,6: 1307-1315	Study design (Active comparator, both groups had stem cells as intervention)
3	Akintoye et al.	2014	Osteonecrosis of the jaw from bone anti-resorptive: impact of skeletal site-dependent mesenchymal stem cells	Oral diseases.2014;20 ; 221–222.	Study design not of interest (Letter to the editor)
4	Ayoyama et al.	2015	Rehabilitation program after mesenchymal stromal cell transplantation augmented by vascularized bone grafts for idiopathic osteonecrosis of the femoral head: a preliminary study	Archives of physical medicine and rehabilitation. 2015; 96: 532-539.	Study design not of interest (case series)
5	Ayoyama et al.	2022	Effect of a Rehabilitation Program After Mesenchymal Stromal Cell Transplantation for Advanced Osteonecrosis of the Femoral Head: A 10-Year Follow-Up Study	Archives of Rehabilitation Research and Clinical Translation. 2022; 4:100179.	Study design not of interest (retrospective study)
6	Ayoyama et al.	2015	Clinical trial for idiopathic osteonecrosis of femoral head by multipotent mesenchymal stromal cells	Japanese Journal of Clinical Medicine. 2015; 73:468-472.	Outcome not of interest (bone regeneration with amelioration of symptoms)
7	Bizot et al.	1998	Femoral head osteonecrosis after bone marrow transplantation	Clinical Orthopaedics and Related Research®. 1998; 357: 127-134.	Study design not of interest (retrospective study)

8	Bizot et al.	1996	Avascular necrosis of the femoral head after allogeneic bone-marrow transplantation. A retrospective study of 27 consecutive THAs with a minimal two-year follow-up	The Journal of Bone & Joint Surgery British Volume. 1996; 78:878-883.	Study design not of interest (retrospective study)
9	BraNon et al.	2007	Influence of acetabular coverage on hip survival after free vascularized fibular grafting for femoral head osteonecrosis	Journal of Bone & Joint Surgery. 2007; 89:448-449.	Study design not of interest (Letter to the editor)
10	Brunelli et al.	1991	Free microvascular fibular transfer for idiopathic femoral head necrosis: long-term follow-up	Journal of reconstructive microsurgery. 1991; 7:285-295.	Study design not of interest (cohort study)
11	Cabrolier et al.	2016	Is instillation of bone marrow stem cells at the time of core decompression useful for osteonecrosis of the femoral head?	Medwave.2016; 16 Suppl 1: e6406.	Study design not of interest (meta-analysis)
12	Colori et al.	2014	Treatment of AVN using the induction chamber technique and a biological-based approach: indications and clinical results	Injury. 2014; 45:369-373.	Study design not of interest (Retrospective study)
13	Cao et al.	2010	Clinical application of minimally invasive core decompression combined with impaction bone grafting to the treatment of femoral head necrosis	Journal of Orthopaedics and Traumatology. 2010; 23:111-113.	Study design (Observational study)
14	Messa et al.	2012	Stem cell implant with neck-head decompression for aseptic necrosis of the femoral head	Acta Ortopédica Mexicana. 2012; 26: 290-297.	Study design not of interest (Case series)
15	Cella et al.	2011	Autologous bone marrow stem cell intralesional transplantation repairing bisphosphonate-related osteonecrosis of the jaw	Head & face medicine. 2011; 7:1-6.	Study design not of interest (Case report)
16	Chang et al.	2010	Treatment of early avascular necrosis of femoral head by core	Chinese Journal of Reparative and	The text obtained after translating is indecipherable

			decompression combined with autologous bone marrow mesenchymal stem cells transplantation	Reconstructive Surgery. 2010; 24:739-743.	
17	Chen et al.	2009	Advance in the combination of Chinese medicine and bone marrow-derived mesenchymal stem cells as treatment for osteonecrosis of the femoral head	Chinese Journal of Integrated Traditional and Western Medicine. 2009; 29:562-565.	Study design not of interest (Review)
18	Chen et al.	2023	Could BMMNCs therapy reduce the mid-and long-term rate of total hip arthroplasty of femoral head necrosis? A systematic review and meta-analysis	Medicine. 2023;102: e34311.	Study design not of interest (meta-analysis)
19	Cheng et al.	2012	Progress of treating hormonal avascular necrosis of the femoral head by Chinese medicine and transplant of human bone marrow mesenchymal stem cells	Chinese Journal of Integrated Traditional and Western Medicine. 2012; 32:1004-1007.	Study design not of interest (Review)
20	Chotivichit et al.	2014	Core decompression with bone marrow injection for the treatment of femoral head osteonecrosis	Journal of the Medical Association of Thailand. 2014; 97: S139-143.	Study design not of interest (Retrospective review)
21	Ciapetti et al.	2016	Effects of hypoxia on osteogenic differentiation of mesenchymal stromal cells used as a cell therapy for avascular necrosis of the femoral head	Cytotherapy.2016;18:1087-1099.	Study design not of interest (in vitro study)
22	Rosenblum et al.	2019	Osteonecrosis of the Femoral Head	Orthopedic Clinics of North America. 2019; 50:139-149.	Study design not of interest (Review)
23	Monas et al.	2013	Autologous concentrated bone marrow graft in the treatment of femoral head avascular necrosis: clinical outcome after two years of follow-up in a non-controlled	Revista Española de CirugíaOrtopédica y Traumatología. 2013; 57:106-110.	Study design not of interest (prospective cohort study)

			prospective study		
24	Cui et al.	2011	Emerging ideas: treatment of pre-collapse osteonecrosis using stem cells and growth factors	Clinical Orthopaedics and Related Research®. 2011; 469:2665-2669.	Study design not of interest (Review)
25	Ding et al.	2013	Free vascularized fibular grafting benefits severely collapsed femoral head in concomitant with osteoarthritis in very young adults: a prospective study	Journal of reconstructive microsurgery. 2013; 29:387-392.	Study design not of interest (prospective cohort study)
26	Dome et al.	2011	Exosomes from Adipose-Derived Stem Cells Can Prevent Medication-Related Osteonecrosis of the Jaw	Medical Science Monitor: International Medical Journal of Experimental and Clinical Research. 2021; 27: e929684.	Study design not of interest (Review)
27	Doring et al.	2020	Longtime Outcome After Intraosseous Application of Autologous Mesenchymal Stromal Cells in Paediatric Patients and Young Adults with Avascular Necrosis After Steroid or Chemotherapy	Stem Cells and Development. 2020; 29:811-822.	Study design not of interest (Retrospective review)
28	Elad et al.	2013	Hematopoietic stem cells and bisphosphonate-related osteonecrosis of the jaw	Oral Diseases. 2012;19(5) :530.	Study design not of interest (Letter to the editor)
29	Elgaz et al.	2020	Mesenchymal stromal cells for osteonecrosis	Journal of translational medicine.2020; 18: 399.	Study design not of interest (systematic review)
30	Emadedin et al.	2019	Autologous bone marrow-derived CD133 cells with core decompression as a novel treatment method for femoral head osteonecrosis: a pilot study	Cryotherapy. 2019; 21: 107-112.	Study design not of interest (quasi experimental study)
31	Erne et al.	2008	Aseptic osteonecrosis of the head of the metacarpal (Mauclaire's	HandchirurgieMikrochirurgie · Plastische	Study design not of interest (case report)

			disease)-case report and review of the literature	Chirurgie.2008; 40: 207-210.	
32	Faraci et al.	2006	Osteonecrosis after allogeneic stem cell transplantation in childhood. A case-control study in Italy	Haematologica.2006; 91:1096-1099.	Study design not of interest (case-control)
33	Gangji et al.	2005	Treatment of osteonecrosis of the femoral head with implantation of autologous bone-marrow cells. Surgical technique	Journal of Bone & Joint Surgery. 2005; 87:106-112.	Study design not of interest (Review)
34	Gangji et al.	2010	Treating osteonecrosis with autologous bone marrow cells	Skeletal radiology. 2010; 39:209-211.	Study design not of interest (Letter to the editor)
35	Gangji et al.	2004	Treatment of osteonecrosis of the femoral head with implantation of autologous bone-marrow cells. A pilot study	Journal of Bone & Joint Surgery. 2004; 86:1153-1160.	Study design not of interest (prospective cohort study)
36	Gao et al.	2016	Combined with Bone Marrow-Derived Cells and rhBMP-2 for Osteonecrosis after Femoral Neck Fractures in Children and Adolescents: A case series	Scientific Reports. 2016; 6:30730.	Study design not of interest (case series)
37	Garcia et al.	2012	Mesenchymal stem cells and bisphosphonate-related osteonecrosis of the jaw: the future?	Oral Diseases. 2012; 18:823-824.	Study design not of interest (Letter to the editor)
38	Garanchi et al.	2019	Biomarkers of bone healing induced by a regenerative approach based on expanded bone marrow-derived mesenchymal stromal cells	Cytotherapy. 2019; 21:870-885.	Outcomes not of interest (regenerative ability of MSCs)
39	Gossamann et al.	1991	Osteonecrosis following short-term, high-dosage steroid therapy	SchweizerischeMedizinischeWochenschrift. 1991; 121: 635-641.	Study design not of interest (Review)
40	He et al.	2016	Comparison of core decompression with stem cell transplantation and tantalum rod implanting in treating stage II non-	China Journal of Orthopaedics and Traumatology. 2016; 29:1119-	Study design not of interest (case control study)

			traumatic osteonecrosis of femoral head	1124.	
41	Hernigou et al.	2021	Cell therapy for posttraumatic shoulder osteonecrosis	Morphologie. 2021; 105:162-169.	Study design not of interest (retrospective review)
42	Hernigou et al.	2021	Cell therapy for post-traumatic hip osteonecrosis in young patients	Morphologie.2021; 105: 127-133.	Study design not of interest (retrospective case control study)
43	Hernigou et al.	2002	Treatment of osteonecrosis with autologous bone marrow grafting	Clinical Orthopaedics and Related Research®. 2002; 405: 14-23.	Study design not of interest (Conference paper)
44	Hernigou et al.	2018	Stem cell therapy in early post-traumatic talus osteonecrosis	International Orthopaedics. 2018; 42: 2949-2956.	Study design not of interest (Cohort study)
45	Hernigou et al.	2017	Allografts supercharged with bone-marrow-derived mesenchymal stem cells possess equivalent osteogenic capacity to that of autograft: a study with long-term follow-ups of human biopsies	International orthopaedics. 2017; 41:127-132.	Stud design not of interest (cohort study)
46	Hernigou et al.	2015	Osteonecrosis repair with bone marrow cell therapies: state of the clinical art	Bone. 2015; 70:102-109.	Study design not of interest (Review)
47	Hernigou et al.	2018	History of concentrated or expanded mesenchymal stem cells for hip osteonecrosis: is there a target number for osteonecrosis repair?	International Orthopaedics. 2018; 42: 1739-1745.	Study design not of interest (Review)
48	Hommaet al.	2014	Supercharging allografts with mesenchymal stem cells in the operating room during hip revision	International orthopaedics. 2014; 38: 2033-2044.	Study design of interest (Observational)
49	Huten et al.	2021	Treatment of aseptic osteonecrosis of the femoral head: Historical aspects	Morphologie. 2021;105: 102-119.	Study design not of interest (Review)

50	Ibrahim et al.	2012	Platelet-rich plasma as a non-surgical treatment option for osteonecrosis	Physical Medicine and Rehabilitation. 2012; 4:1015-1019.	Study design not of interest (case report)
51	Jagasia et al.	2010	Age and total-body irradiation in addition to corticosteroid dose are important risk factors for avascular necrosis of the bone	Biology of Blood and Marrow Transplantation. 2010; 16:1750-1751.	Study design not of interest (Letter to the editor)
52	Jayaramaraj u et al.	2019	Impaction Bone Grafting and Valgus Osteotomy: A Technical Trick for the Treatment of Femoral Neck Non-unions	Journal of Orthopaedic Trauma. 2019; 33: e403-408.	Population not of interest (femoral neck Non unions, Different disease)
53	Jazrawi et al.	1999	Catastrophic failure of a cemented, collarless, polished, tapered cobalt-chromium femoral stem used with impaction bone-grafting. A report of two cases	Journal of bone and joint surgery. 1999; 81: 844-847.	Study design not of interest (case report)
54	Jeyarama et al.	2021	Autologous bone marrow-derived mesenchymal stem cell therapy for osteonecrosis of femoral head: A systematic overview of overlapping meta-analyses	Journal of Clinical Orthopaedicsand Trauma. 2021; 13:134-142.	Study design not of interest (Systematic review)
55	Ji et al.	2008	Three-tunnels core decompression with implantation of bone marrow stromal cells (bMSCs) and decalcified bone matrix (DBM) for the treatment of early femoral head necrosis	China Journal of Orthopaedics and Traumatology. 2008; 21:776-778.	Study design not of interest (retrospective study)
56	Jones et al.	2008	Cell-based therapies for osteonecrosis of the femoral head	Biology of Blood and Marrow Transplantation. 2008; 14:1081-1087.	Study design not of interest (Review)
57	Jones et al.	2009	Outcome measures for evaluation of treatments for osteonecrosis	Orthopaedic Clinics of North America. 2009;40: 179-191.	Study design not of interest (Review)

58	Kakar et al.	2011	Role of vascularized bone grafts in the treatment of scaphoid Non unions associated with proximal pole avascular necrosis and carpal collapse	Journal of Hand Surgery. 2011; 36:722-725.	Study design not of interest (Review)
59	Kawate et al.	2006	Tissue-engineered approach for the treatment of steroid-induced osteonecrosis of the femoral head: transplantation of autologous mesenchymal stem cells cultured with beta-tricalcium phosphate ceramics and free vascularized fibula	Artificial organs. 2006; 30:960-962.	Study design not of interest (case report)
60	Kim et al.	2012	Autologous adipose tissue-derived stem cells induce persistent bone-like tissue in osteonecrotic femoral heads: not bone-like, but fat-like tissue	Pain Physician. 2012; 15: E749.	Study design not of interest (Letter to the editor)
61	Kim et al.	2021	Long-Term Results of Total Hip Arthroplasty in Young Patients with Osteonecrosis After Allogeneic Bone Marrow Transplantation for Hematological Disease: A Multicenter, Propensity-Matched Cohort Study with a Mean 11-Year Follow-Up	The Journal of Arthroplasty. 2021; 36:1049-1054.	Study design not of interest (cohort study)
62	Kuhlen et al.	2020	Guidance to Bone Morbidity in Children and Adolescents Undergoing Allogeneic Hematopoietic Stem Cell Transplantation	Transplantation. 2020; 26::e27-37.	Study design not of interest (Review)
63	Kuroda et al.	2020	Recombinant human FGF-2 therapy for osteonecrosis of the femoral head: 5-year follow-up	Regenerative Medicine. 2020; 15: 2261-2271.	Intervention is not of interest (Recombinant human fgf-2 therapy)
64	Kuroda et al.	2016	Joint-preserving regenerative therapy for patients with early-stage osteonecrosis of the	Inflammation and regeneration. 2016; 36:1-8.	Study design not of interest (review)

			femoral head		
65	Lecroy et al.	2002	Free vascularized fibular bone grafting in the management of femoral neck Non-union in patients younger than fifty years	Journal of orthopaedic trauma. 2002; 16:464-472.	Population not of interest (femoral neck non union, Different disease)
66	Lee et al.	2003	Multipotential mesenchymal stem cells from femoral bone marrow near the site of osteonecrosis	Stem cells. 2003; 21:190-199.	Study design not of interest (in vitro study)
67	Sun et al.	2023	Efficacy of Modified Lightbulb Technique by Percutaneous Femoral Neck-Head Fenestration Combined with Compacted Artificial Bone Graft for Treating Precollapse Osteonecrosis of the Femoral Head	The Journal of arthroplasty. 2023; 38:1760–1766.	Study design not of interest (Retrospective study)
68	Li et al.	2018	Stem cell therapy for treating osteonecrosis of the femoral head: From clinical applications to related basic research	Stem cell research & therapy. 2018; 9:1-11.	Study design not of interest (Review)
69	Li et al.	2015	A study of autologous stem cell therapy assisted regeneration of cartilage in avascular bone necrosis	European review for medical and pharmacological sciences.2019; 19:3833–3837.	Study design not of interest (case studies)
70	Liang et al.	2023	Clinical outcomes of autologous platelet-rich plasma and bone marrow mononuclear cells grafting combined with core decompression for Association Research Circulation Osseous II- IIIA stage non-traumatic osteonecrosis of the femoral head	International orthopaedics.2023; 47:2181–2188.	Study design not of interest (retrospective review)
71	Liang et al.	2013	Scaphoid Non-union reconstructed with vascularized bone-grafting pedicled on 1,2 intercompartmental supra retinacular artery and external fixation	European review for medical and pharmacological sciences.2013; 17:1447–1454.	Study design not of interest (Retrospective review)

72	Lim et al.	2013	Stem cell implantation for osteonecrosis of the femoral head	Experimental & molecular medicine, 45(11), e61.	Study design not of interest (retrospective review)
73	Liu et al.	2009	Treatment for osteonecrosis of femoral head by hVEGF-165 gene modified marrow stromal stem cells under arthroscope	National Medical Journal of China.2009; 89:2629-2633.	Study design not of interest (Animal study)
74	Liu et al.	2018	Investigating clinical failure of core decompression with autologous bone marrow mononuclear cells grafting for the treatment of non - traumatic osteonecrosis of the femoral head	International Orthopaedics. 2018; 42:1575-1583.	Outcome not of interest (factor responsible for failure of BMMCG)
75	Liu et al.	2013	Efficacies of bone-marrow-derived mononuclear cells with a hydroxylapatite composite in the treatment of osteonecrosis of the femoral head	National Medical Journal of China. 2013; 93:2126-2130	The text obtained after translating is indecipherable
76	Lovecchio et al.	2017	Avascular Necrosis Is Associated with Increased Transfusions and Readmission Following Primary Total Hip Arthroplasty	Orthopedics. 2017; 40:171-176.	Study design not of interest (database study)
77	Lyu et al.	2023	Core decompression with β-tri-calcium phosphate grafts in combination with platelet-rich plasma for the treatment of avascular necrosis of femoral head	BioMed Central Musculoskeletal Disorders. 2023;24:40	Study design not of interest (cohort study)
78	Ma et al.	2021	Core Decompression with Local Administration of Zoledronate and Enriched Bone Marrow Mononuclear Cells for Treatment of Non-Traumatic Osteonecrosis of Femoral Head	Orthopaedic Surgery. 2021; 13:1843-1852.	Study design not of interest (retrospective review)

79	Mao et al.	2015	The efficacy of targeted intraarterial delivery of concentrated autologous bone marrow containing mononuclear cells in the treatment of osteonecrosis of the femoral head: a five-year follow-up study	Bone. 2013; 57:509-516.	Study design not of interest (cohort study)
80	Marcianik et al.	2005	Osteonecrosis of the femoral head. A study of 101 hips treated with vascularized fibular grafting	Journal of Bone and Joint surgery. 2005; 87:742-747.	Study design not of interest (cohort study)
81	Marsell et al.	2014	Successful treatment of a humeral capitulum osteonecrosis with bone morphogenetic protein-7 combined with autologous bone grafting	Upsala Journal of Medical Sciences. 2014; 119:287-289.	Study design not of interest (case report)
82	Martin et al.	2013	Use of concentrated bone marrow aspirate and platelet-rich plasma during minimally invasive decompression of the femoral head in the treatment of osteonecrosis	Croatian medical journal. 2013; 54:219-224.	Study design not of interest (opinion paper)
83	Maruyama et al.	2018	The effects of a functionally graded scaffold and bone marrow-derived mononuclear cells on steroid-induced femoral head osteonecrosis	Biomaterials. 2018; 187:39-46.	Study design not of interest (Animal study)
84	Marx et al.	2009	Reconstruction of defects caused by bisphosphonate-induced osteonecrosis of the jaws	Journal of oral and maxillofacial surgery. 2009; 67:107-119.	Study design not of interest (case reports)
85	Mascarin et al.	1991	Avascular necrosis of bone in children undergoing allogeneic bone marrow transplantation	Cancer. 1991; 68:655-659.	Study design not of interest (case reports)
86	Mastuura et al.	2016	Therapeutic interactions between mesenchymal stem cells for healing medication-related osteonecrosis of the jaw	Stem cell research & therapy. 2016; 7:1-11.	Study design not of interest (Animal study)

87	Mawardi et al.	2016	Hematopoietic Cell Transplantation in Patients with Medication-Related Osteonecrosis of the Jaws	Biology of Blood and Marrow Transplantation. 2016; 22:344-348.	Study design not of interest (Retrospective chart review)
88	Mcavoy et al.	2010	Corticosteroid dose as a risk factor for avascular necrosis of the bone after hematopoietic cell transplantation	Biology of Blood and Marrow Transplantation. 2010; 16:1231-1236.	Study design not of interest (case-control study)
89	Mcclune et al.	2012	Bone loss and avascular necrosis of bone after hematopoietic cell transplantation	Seminars in hematology 2012; 49:59-65	Study design not of interest (Review)
90	Mcdonald et al.	2013	Development of an evidence-based clinical guideline for age-appropriate screening, prevention, and management of bone abnormalities in children post-hematopoietic stem cell transplant	Journal of Pediatric Hematology/ Oncology Nursing. 2013; 30: 78-89.	Study design not of interest (Review)
91	Meermans et al.	2020	CORR Insights®: Did Osteoblastic Cell Therapy Improve the Prognosis of Pre-fracture Osteonecrosis of the Femoral Head? A Randomized Controlled Trial	Clinical Orthopaedics and Related Research. 2020;478:1316-1318	Study design not of interest (Comment)
92	Mishima et al.	2016	The safety and efficacy of combined autologous concentrated bone marrow grafting and low-intensity pulsed ultrasound in the treatment of osteonecrosis of the femoral head	European Journal of Orthopaedic Surgery & Traumatology. 2016; 26:293-298.	Study design not of interest (observational cohort study)
93	Mitsuzawa et al.	2022	Corticosteroid-associated osteonecrosis of the femoral head after orthotopic liver transplantation and the outcomes of subsequent total hip arthroplasty	Journal of Orthopaedic Science. 2022; 27:395-401.	Study design not of interest (Retrospective analysis)

94	Mont et al.	2003	Outcome of Non vascularized bone grafting for osteonecrosis of the femoral head	Clinical Orthopaedics and Related Research. 2003;417:84-92.	Study design not of interest (review)
95	Mont et al.	2000	Survival analysis of hips treated with core decompression or vascularized fibular grafting because of avascular necrosis	Journal of bone and joint surgery. American volume. 2000; 82:290-291.	Study design not of interest (Comment)
96	Mont et al.	2007	Core decompression and non-vascularized bone grafting for the treatment of early-stage osteonecrosis of the femoral head	Instructional course lectures.2007; 56:213-220.	Study design not of interest (Review)
97	Mori et al.	2001	Avascular necrosis in the femoral head secondary to bone marrow infarction in a patient with graft-versus-host disease after unrelated bone marrow transplantation	Annals of hematology. 2001; 80:238-242.	Study design not of interest (case report)
98	Mucke et al.	2009	Bisphosphonate related osteonecrosis of the jaws treated by surgical resection and immediate osseous microvascular reconstruction	Journal of Cranio-Maxillofacial Surgery. 2009; 37:291-297.	Study design not of interest (Case report)
99	Muller et al.	2009	Secretion of angiogenic proteins by human multipotent mesenchymal stromal cells and their clinical potential in the treatment of avascular osteonecrosis	Leukemia. 2008; 22:2054-2061.	Study design not of interest (in vitro comparative study)
100	Mundo et al.	2006	Multifocal avascular necrosis after liver transplantation: an unusual presentation of the antiphospholipid syndrome	Lupus. 2006; 15:304-307.	Study design not of interest (case report)
101	Murakami et al.	2004	A long-term follow-up study of four cases who underwent curettage and autogenous bone grafting for steroid-related	The Kurume Medical Journal. 2004; 51:277-281.	Study design not of interest (case report)

			osteonecrosis of the femoral condyle		
102	Murena et al.	2014	Treatment of humeral shaft aseptic Non unions in elderly patients with opposite structural allograft, BMP-7, and mesenchymal stem cells	Orthopedics. 2014; 37:e201-e206.	Study design not of interest (case report)
103	Nagi et al.	1992	Fibular osteosynthesis for delayed type II and type III femoral neck fractures in children	Journal of orthopaedic trauma. 1992; 6(3):306-313.	Intervention is not of interest (Fibular graft and cancellous lag screw)
104	Nally et al.	2018	THA conversion rate comparing decompression alone, with autologous bone graft or stem cells in osteonecrosis	Hip International. 2018; 28:189-193.	Study design not of interest (electronic database study)
105	Namazi et al.	2012	Autologous adipose tissue-derived stem cells induce persistent bone-like tissue in osteonecrotic femoral heads: a molecular mechanism	Pain physician. 2012; 15:E345.	Study design not of interest (Letter to the editor)
106	Nandeesh et al.	2016	Treatment of AVN Using Autologous BM Stem Cells and Activated Platelet-Derived Growth Factor Concentrates	Journal of Stem Cells. 2016;11:135-148.	Outcome not of interest
107	Napora et al.	2018	Early MRI Detection and Closed Bone Graft Epiphysiodesis May Alter the Course of Avascular Necrosis Following Unstable Slipped Capital Femoral Epiphysis	Journal of Pediatric Orthopaedics. 2018; 38:202-207.	Study design not of interest (retrospective study)
108	Nasser et al.	2018	Lesson of the week: Depot corticosteroid treatment for hay fever causing avascular necrosis of both hips	British Medical Journal. 2001; 322:1589-1591.	Study design not of interest (case report)
109	Ninimaki et al.	2019	The radiological and clinical follow-up of osteonecrosis in cancer patients	Acta oncologica. 2019; 58:505-511.	Study design (non-randomized controlled clinical trial)

110	Nishitani et al.	2021	Long-Term Survivorship and Clinical Outcomes of Osteochondral Autologous Transplantation for Steroid-Induced Osteonecrosis of the Knee	Cartilage. 2021; 13:1156S-1164S.	Study design not of interest (case series)
111	Nishi et al.	2020	Surgical Management of Medication-Related Osteonecrosis of the Jaw Patients Related to Dental Implants	Journal of Craniofacial Surgery. 2020; 31:1037-1041.	Study design not of interest (retrospective study)
112	Nishi et al.	2022	Medication-Related Osteonecrosis of the Jaw Associated in a Patient Treated with Etanercept	Journal of Craniofacial Surgery. 2022; 33:e694-706.	Study design not of interest (Case report)
113	Osawa et al.	2021	Long-term outcomes of curved intertrochanteric varus osteotomy combined with bone impaction grafting for non-traumatic osteonecrosis of the femoral head	The Bone & Joint Journal. 2021; 103:665-671.	Study design not of interest (Comparative study)
114	Otto et al.	2021	Infection as an Important Factor in Medication-Related Osteonecrosis of the Jaw (MRONJ)	Medicina. 2021; 57:463.	Study design not of interest (Review)
115	Ozdemir et al	2022	Long-term follow-up of 96 patients younger than age 25 with 119 primary cemented total hip arthroplasties	Acta Orthopaedica. 2023; 94:102.	Study design not of interest (Cohort study)
116	Ozdemir et al.	2022	Comparison of clinical outcomes of autologous bone graft versus pronator quadratus pedicled vascularized bone graft in the treatment of scaphoid Non union	Acta Orthopædica Belgica. 2023; 88:447-455.	Population is not of interest (Treatment of scaphoid non-union)
117	Ozkam et al.	2017	The Efficacy Of 1,2-Intercompartmental Supraretinacular Artery Pedicled Vascularised Bone Graft for Scaphoid Proximal End Non -Union And Avascular Necrosis	Acta orthopaedica Belgica. 2017; 83:589-598.	Study design not of interest (retrospective study)

118	Ozturk et al	2022	Clinical results of free vascularized fibula graft in the management of precollapse osteonecrosis of the femoral head: A retrospective clinical study	Acta Orthopaedica et Traumatologica Turcica. 2022; 56:105-110	Study design not of interest (retrospective study)
119	Padhye et al.	2016	Incidence and outcome of osteonecrosis in children and adolescents after intensive therapy for acute lymphoblastic leukemia (ALL)	Cancer Medicine. 2016; 5:960-967.	Study design not of interest (retrospective study)
120	Pak et al.	2021	Endoscopic observation finding in the core decompression procedure of osteonecrosis of femoral head and effect of additional treatments	International Orthopaedics. 2021; 45:95-99.	Study design not of interest (Case series)
121	Pak et al.	2012	Autologous adipose tissue-derived stem cells induce persistent bone-like tissue in osteonecrotic femoral heads	Pain physician. 2012;15:75-85	Study design not of interest (case report)
122	Pak et al.	2014	Complete resolution of avascular necrosis of the human femoral head treated with adipose tissue-derived stem cells and platelet-rich plasma	Journal of international medical research. 2014; 42:1353-1362.	Study design not of interest (case report)
123	Palekar et al.	2021	Hip Preservation with Autologous Osteoblast Cell-Based Treatment in Osteonecrosis of the Femoral Head	Orthopedics. 2021; 44:e183-189.	Study design not of interest (Observational cohort study)
124	Papanagitou et al.	2014	Autologous (Non - vascularised) fibular grafting with recombinant bone morphogenetic protein-7 for the treatment of femoral head osteonecrosis: preliminary report	The Bone & Joint Journal. 2014; 96:31-35.	Study design not of interest (Report)
125	Persiana et al.	2015	Stage-related results in treatment of hip osteonecrosis with core-decompression and autologous mesenchymal	Acta Orthop Belg. 2015; 81:406-412.	Study design not of interest (observational cohort study)

			stem cells		
126	Petropoulou et al.	2010	Prospective assessment of bone turnover and clinical bone diseases after allogeneic hematopoietic stem-cell transplantation	Transplantation. 2010; 89:1354-1361.	Population is not of interest (bone diseases)
127	Petsatodis et al.	2009	Cementless total hip arthroplasty for osteonecrosis of the femoral head after allogenic bone marrow transplantation	The Journal of Arthroplasty. 2009; 24:414-420.	Study design not of interest (not a clinical trial)
128	Poggio et al.	2006	Surgical treatment for vascular necrosis of femoral head after hematopoietic stem cell transplantation	Medicina Clinica. 2006; 127:738-740.	Study design not of interest (Observational Cohort study)
129	Pozzi et al.	2009	Bisphosphonates-associated osteonecrosis of the jaw: A long-term follow-up of a series of 35 cases observed by GISL and evaluation of its frequency over time	American journal of hematology. 2009; 84:850-852	Study design not of interest (Case series)
130	Pucher et al.	2000	The value of distal greater trochanteric transfer in the treatment of deformity of the proximal femur owing to avascular necrosis	Journal of Pediatric Orthopaedics. 2000; 20:311-316.	Study design not of interest (Case series)
131	Qiu et al.	2021	Protective Effect of Human Umbilical Cord Mesenchymal Stem Cells in Glucocorticoid-induced Osteonecrosis of Femoral Head	Current Medical Science. 2021; 41:909-915.	Study design not of interest (Animal model)
132	Rackwitz et al.	2012	Stem cell- and growth factor-based regenerative therapies for avascular necrosis of the femoral head	Stem cell research & therapy. 2012; 3:1-9.	Study design not of interest (Review)
133	Richard et al.	2021	Outcomes of free vascularized fibular graft for post-traumatic osteonecrosis of the femoral head	Injury. 2021; 52:3653-3659.	Study design not of interest (retrospective review)
134	Rochi et al.	2020	Core decompression with bone chips allograft in combination with fibrin	Hip International. 2020; 30: 3-12.	Study design not of interest (retrospective

			platelet-rich plasma and concentrated autologous mesenchymal stromal cells, isolated from bone marrow: results for the treatment of avascular necrosis of the femoral head after 2 years minimum follow-up		study)
135	Saxby et al.	2013	Surgical management of benign idiopathic osteonecrosis of the external auditory canal	Operationas Research Letters. 2013; 75:257-264.	Study design not of interest (retrospective case series)
136	Schreiber et al.	1982	Treatment of femur head necrosis using a total hip prosthesis following kidney transplantation	Zeitschrift fur Orthopadie und IhreGrenzgebiete. 1982; 120:868-873.	Intervention is not of interest (total hip prosthesis)
137	Schulte et al.	2004	Avascular osteonecrosis after allogeneic hematopoietic stem-cell transplantation: diagnosis and gender matter	Transplantation. 2004; 78:1055-1063.	Study design not of interest (cohort study)
138	Schulte et al.	2005	Low pretransplant bone-mineral density and rapid bone loss do not increase risk for avascular osteonecrosis after allogeneic hematopoietic stem cell transplantation	Transplantation. 2005; 79:1748-1755.	Study design not of interest (cohort study)
139	Seth et al.	2010	Outcomes of vascularized bone graft reconstruction of the mandible in bisphosphonate-related osteonecrosis of the jaws	The Laryngoscope. 2010; 120:2165-2171.	Study design not of interest (Case series)
140	Seyler et al.	2008	Non vascularized bone grafting defers joint arthroplasty in hip osteonecrosis	Clinical orthopaedics and related research. 2008; 466:1125-1132.	Study design not of interest (retrospective study)
141	Sharma et al.	2012	Osteonecrosis in children after allogeneic hematopoietic cell transplantation: study of prevalence, risk factors and longitudinal changes using MR imaging	Bone marrow transplantation. 2012; 47: 1067-1074.	Study design not of interest (retrospective study)

142	Sharma et al.	2011	Prevalence of osteonecrosis and associated risk factors in children before allogeneic BMT	Bone marrow transplantation. 2011; 46:813-819.	Study design not of interest (retrospective study)
143	Shih et al.	2009	One-stage hip arthroplasty and bone grafting for bilateral femoral head osteonecrosis	Clinical Orthopaedics and Related Research®. 2009; 467:1522-1528.	Study design not of intrest (Observational study)
144	Sionek et al.	2018	Hip osteonecroses treated with calcium sulfate-calcium phosphate bone graft substitute have different results according to the cause of osteonecrosis: alcohol abuse or corticosteroid-induced	International Orthopaedics. 2018; 42:1491-1498.	Study design not of interest (Prospective comparative study)
145	Sixou et al.	1995	Symptomatic osteonecrosis in recipients of Non autologous bone marrow transplants	Revue du Rhumatisme. 1995; 62: 359-363.	Study design not of interest (Retrospective study)
146	Sorich et al.	2015	Osteonecrosis of the Hip in Hematologic Disease: A Review of Conditions and Treatment Options	Journal of long-term effects of medical implants. 2015;25:253-268	Study design not of interest (Review)
147	Spinelli et al.	2017	Microsurgical reconstruction after bisphosphonate-related osteonecrosis of the jaw: our experience with fibula free flap	Journal of Craniofacial Surgery. 2014; 25:788-792.	Study design not of interest (Retrospective study)
148	Statz et al.	2021	Outcomes of shoulder arthroplasty in haematopoietic stem cell transplant patients	International Orthopaedics. 2017; 41:2555-2564.	Study design not of interest (Retrospective study)
149	Street et al	2021	Atraumatic Medullary Osteonecrosis of the Tibia and Femur Treated with Intraosseous Ortho biologics	Cureus. 2021; 27: e16677.	Study design not of interest (case report)
150	Sun et al.	2019	Impacting bone graft via surgical hip dislocation approach versus core	Chinese Journal of Reparative and	Study design not of interest (Retrospective

			decompression and bone graft for avascular necrosis of femoral head at ARCO stage Ⅲ	Reconstructive Surgery. 2019; 33: 531-536.	study)
151	Sun et al.	2016	Focused extracorporeal shock wave for osteonecrosis of the femoral head with leukemia after allo-HSCT: a case series	Bone Marrow Transplantation. 2016; 51: 1507-1509.	Study design not of interest (case series)
152	Sun et al.	2009	The effect of bone marrow mononuclear cells on vascularization and bone regeneration in steroid-induced osteonecrosis of the femoral head	Joint Bone Spine. 2009; 76: 685-690.	Study design not of interest (Animal model)
153	Talamo et al.	2005	Avascular necrosis of femoral and/or humeral heads in multiple myeloma: results of a prospective study of patients treated with dexamethasone-based regimens and high-dose chemotherapy	Journal of Clinical Oncology. 2005; 23: 5217-5223.	Intervention not of interest (Thalidomide)
154	Tauchmano và et al.	2003	Avascular necrosis in long-term survivors after allogeneic or autologous stem cell transplantation: a single center experience and a review	Cancer. 2003; 97: 2453-2461.	Study design not of interest (Review)
155	Then et al.	2012	Incidence and risk factors of bisphosphonate- related osteonecrosis of the jaw in multiple myeloma patients having undergone autologous stem cell transplantation	Onkologie. 2012; 35: 658-664.	Study design not of interest (Retrospective study)
156	Tong et al.	2014	Treatment of Non - traumatic femoral head avascular necrosis by perfusion of bone marrow stromal stem cells through optional artery	China Journal of Orthopaedics and Traumatology. 2014; 27: 565-569.	Study design not of interest (observational cohort study)
157	Torri et al.	2001	Osteonecrosis of the femoral head after allogeneic bone marrow transplantation	Clinical Orthopaedics and Related Research. 2001;	Study design not of interest (Retrospective study)

				382: 124-132.	
158	Trumble et al.	1990	Avascular necrosis after scaphoid fracture: a correlation of magnetic resonance imaging and histology	The Journal of hand surgery. 1990; 15: 557-564.	Intervention is not of interest (MRI)
159	Tzaribachev et al.	2008	Mesenchymal stromal cells: a novel treatment option for steroid-induced avascular osteonecrosis	The Israel Medical Association journal. 2008; 10: 232-234.	Study design not of interest (Review)
160	Varadarajan et al.	2012	Hematopoietic progenitor cell transplantation toxicities in multiple myeloma patients with bisphosphonate-induced osteonecrosis of the jaw: a longitudinal cohort study	Support Care Cancer. 2012; 20: 2969-2975.	Study design not of interest (cohort study)
161	Voss et al.	2017	Treatment of stage II medication-related osteonecrosis of the jaw with necrosectomy and autologous bone marrow mesenchymal stem cells	Odontology. 2017; 105: 484-493	Study design not of interest (cohort study)
162	Wang et al.	2010	Treatment of Non traumatic osteonecrosis of the femoral head with the implantation of core decompression and concentrated autologous bone marrow containing mononuclear cells	Archives of orthopaedic and trauma surgery. 2010; 130: 859-865.	Study design not of interest (cohort study)
163	Xia et al.	2020	Comparison of surgical dislocation and impacting bone graft and surgical dislocation and rotational osteotomy for the treatment of ARCO III femoral head necrosis	Medicine (Baltimore). 2020; 99: e20215	Study design not of interest (Retrospective study)
164	Xian et al.	2020	Platelet-Rich Plasma-Incorporated Autologous Granular Bone Grafts Improve Outcomes of Post-Traumatic Osteonecrosis of the Femoral Head	The Journal of Arthroplasty. 2020; 35: 325-330	Study design not of interest (Cohort study)

165	Xie et al.	2019	Retrospective Long-Term Follow-Up Survival Analysis of the Management of Osteonecrosis of the Femoral Head with Pedicled Vascularized Iliac Bone Graft Transfer	The Journal of arthroplasty. 2019 ;34: 1585-1592.	Study design not of interest (Retrospective study)
166	Xu et al.	2021	Cotransplantation of mesenchymal stem cells and endothelial progenitor cells for treating steroid-induced osteonecrosis of the femoral head	Stem cells translational medicine. 2021; 10: 781-796.	Study design not of interest (Animal study)
167	Yamasaki et al.	2010	Bone-marrow-derived mononuclear cells with a porous hydroxyapatite scaffold for the treatment of osteonecrosis of the femoral head: a preliminary study	The Journal of Bone & Joint Surgery British Volume. 2010; 92: 337-341.	Study design not of interest (retrospective review)
168	Yang et al.	2007	Clinical study on the improvement of ischemia condition with stem cell transplantation in 122 cases necrosis of femoral head	Chinese Journal of Surgery. 2007; 45: 1428-1431.	Study design not of interest (case report)
169	Yang et al.	2022	Efficacy of robot-assisted core decompression combined with human umbilical cord-derived mesenchymal stem cell transplantation for osteonecrosis of the femoral head	European Review for Medical & Pharmacological Sciences. 2022; 26: 4197-4206.	Study design not of interest (Retrospective study)
170	Yasunaga et al.	2007	Treatment of osteonecrosis of the femoral head with implantation of autologous bone-marrow mononuclear cells	Clinical Calcium. 2007; 17: 910-915.	Study design not of interest (Review)
171	Zeng et al.	2015	One-sided hip-preserving and concurrent contralateral total hip arthroplasty for the treatment of bilateral osteonecrosis of the femoral head in different	BioMed Central musculoskeletal disorders. 2015; 16: 1-9.	Study design not of interest (Retrospective study)

			stages: short-medium term outcomes		
172	Zeng et al.	2013	Vascularised greater trochanter bone graft, combined free iliac flap and impaction bone grafting for osteonecrosis of the femoral head	International orthopaedics. 2013; 37: 391-398.	Study design not of interest (cohort study)
173	Zhang et al.	2011	Free vascularised fibular graft for post-traumatic osteonecrosis of the femoral head in teenage patients	The Journal of Bone & Joint Surgery British Volume. 2011; 93: 1314-1319.	Study design not of interest (Retrospective study)
174	Zhang et al.	2008	Progress of vascularized bone grafting for the treatment of avascular osteonecrosis of the femoral head	China journal of orthopaedics and traumatology. 2008; 21: 556-558.	Study design not of interest (Review)
175	Zhang et al.	2009	Therapeutic progress of avascular osteonecrosis of the femoral head using a fibular graft by vascular anastomosis	China journal of orthopaedics and traumatology. 2009; 22:76-78.	Study design not of interest (Review)
176	Zhang et al.	2022	Avascular Osteonecrosis of the Talus: Current Treatment Strategies	Foot & Ankle International. 2022; 43:291-302.	Study design not of interest (Review)
177	Zhao et al.	2019	The Combined Therapy of Tantalum Rod Implantation and Vascularized Bone Transplantation for Femoral Head Osteonecrosis: A Retrospective Long-Term Follow-Up Survival Analysis	Surgical Technology International. 2019; 35: 406-409.	Study design not of interest (Retrospective study)
178	Zhao et al.	2012	Combined vascularized iliac and greater trochanter graftings for reconstruction of the osteonecrosis femoral head with collapse: reports of three cases with 20 years follow-up	Microsurgery. 2012; 32: 546-551.	Study design not of interest (case study)
179	Zhao et al.	2020	Clinical Follow-up Study of the Reconstruction of the Femoral Head with	Annals of Plastic Surgery. 2020; 84: S215-S221.	Study design not of interest (cohort study)

			Transferred Vascularized Greater Trochanter Bone Graft for Association Research Circulation Osseous III-IV Osteonecrosis of the Femoral Head		
180	Zhao et al.	2010	Will a vascularized greater trochanter graft preserve the necrotic femoral head?	Clinical Orthopaedics and Related Research. 2010; 468: 1316-1324.	Study design not of interest (Retrospective study)
181	Zhao et al.	2005	Comparison of total hip replacement and transplantation of vascularized bone graft in treating late ischemic necrosis of the femoral head	Chinese journal of reparative and reconstructive surgery. 2005; 19: 700-702.	Study design not of interest (cohort study)
182	Zhao et al.	2007	Treatment of osteonecrosis of femoral head with minimally invasive vascularized bone grafting	Zhonghua yixue za zhi. 2007; 87:2036-2040.	Study design not of interest (cohort study)
183	Zhao et al.	2023	Effects of Puerarin- Loaded Tetrahedral Framework Nucleic Acids on Osteonecrosis of the Femoral Head	Small. 2023; 19: e2302326.	Study design not of interest (In vitro study)
184	Zhun et al.	2018	Efficiency of Cell Therapy to GC-Induced ONFH: BMSCs with Dkk-1 Interference Is Not Superior to Unmodified BMSCs	Stem Cells International. 2018; 2018: 1340252.	Study design not of interest (In vitro study)
185	Zuo et al.	2016	Effectiveness Of Bone Grafting Through Windowing at Femoral Head-Neck Junction for Treatment of Osteonecrosis with Segmental Collapse of Femoral Head	Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi. 2016; 30: 397-401.	Study design not of interest (retrospective study
186	Alpigiani et al.	2013	Use of bone marrow cells (BMCS) added to platelet-rich plasma (PRP) for treatment of bone degenerative processes in jia patient: 18-month	Annals of Rheumatic Diseases. 2013; 71: 704.	Study design not of interest (Case report)

			follow-up		
187	Andronic et al.	2021	Lack of Conclusive Evidence of the Benefit of Biologic Augmentation in Core Decompression for Non traumatic Osteonecrosis of the Femoral Head: A Systematic Review	The Journal of Arthroscopic & Related Surgery. 2021; 37: 3537-3551.	Study design not of interest (Review)
188	Atilla et al.	2019	Joint-preserving procedures for osteonecrosis of the femoral head	EFORT open reviews. 2019; 4: 647-658	Study design not of interest (Review)
189	Badros et al.	2006	Osteonecrosis of the jaw in multiple myeloma patients: Clinical features and risk factors	Journal of clinical oncology. 2006; 24: 945-952.	Study design not of interest (Review)
190	Bamias et al.	2010	Avascular osteonecrosis of the jaw as a side effect of bisphosphonate treatment	Oncology Research and Treatment. 2010; 33:288-289.	Study design not of interest (Review)
191	Bhatia et al.	2011	Long-term health impacts of hematopoietic stem cell transplantation inform recommendations for follow-up	Expert review of hematology. 2011; 4: 437-454.	Study design not of interest (Review)
192	Bi et al.	2014	Different artificial bones combined with bone marrow mesenchymal stem cell therapy for early osteonecrosis of the femoral head: Controversy and progress	Chinese Journal of Tissue Engineering Research. 2014; 18:1957.	Study design not of interest (Review)
193	Biltiau et al.	2008	Stem cell therapy for osteonecrosis of the femoral head	Current pain and headache reports. 2018; 22: 1-9.	Study design not of interest (Review)
194	Bolton et al.	2009	Osteonecrosis of the elbow following bisphosphonate treatment	In rheumatology. 2009; 48: I116-I116.	Study design not of interest (Case report)
195	Calori et al.	2014	Treatment of AVN using the induction chamber technique and a biological-based approach: Indications and clinical results	Injury. 2014; 45: 369-373.	Study design not of interest (retrospective study

196	Campbell et al.	2009	Predictors of avascular necrosis of bone in long-term survivors of hematopoietic cell transplantation	Cancer. 2009; 115: 4127-4135.	Study design not of interest (retrospective study)
197	Campbell et al.	2016	Mesenchymal Stem Cell Alterations in Bone Marrow Lesions in Patients with Hip Osteoarthritis	Arthritis & Rheumatology. 2016; 68: 1648-1659.	Population not of interest (Osteoarthritis, Different disease)
198	Cao et al.	2021	Reciprocal effect of microRNA-224 on osteogenesis and adipogenesis in steroid-induced osteonecrosis of the femoral head	Bone. 2021; 145: e115844.	Intervention not of interest (Gene therapy)
199	Cenni et al.	2011	Idiopathic and secondary osteonecrosis of the femoral head show different thrombophilic changes and normal or higher levels of platelet growth factors	Acta Orthopaedica. 2011; 82: 42-49.	Study design not of interest (cohort study)
200	Cerza et al.	2012	Treatment of avascular necrosis with stem cells under arthroscopic control	Journal of orthopaedics and Traumatology.2012;13:S107	Study design not of interest (conference presentation)
201	Chalmers et al.	2017	What Risks are Associated with Primary THA in Recipients of Hematopoietic Stem Cell Transplantation?	Clinical Orthopaedics and Related Research. 2017; 475: 475-480.	Study design not of interest (observational study)
202	Che et al.	2022	Emerging roles of growth factors in osteonecrosis of the femoral head	Frontiers in Genetics. 2022; 13: 1037190.	Intervention not of interest (Gene therapy)
203	Chen et al.	2023	Engineered Exosome-Functionalized Extracellular Matrix-Mimicking Hydrogel for Promoting Bone Repair in Glucocorticoid-Induced Osteonecrosis of the Femoral Head	American Chemical Society Applied Materials & Interfaces. 2023; 15: 28891-28906.	Intervention not of interest (gene therapy)
204	Chen et al.	2016	Efficacy of umbilical cord-derived mesenchymal stem cell-based therapy for osteonecrosis of the femoral head: A three-	Molecular Medicine Reports. 2016; 14: 4209-4215.	Study design not of interest (retrospective study)

			year follow-up study		
205	Chen et al.	2020	Extracellular vesicles from human urine- derived stem cells inhibit glucocorticoid-induced osteonecrosis of the femoral head by transporting and releasing pro-angiogenic DMBT1 and anti-apoptotic TIMP1	Acta Biomaterialia. 2020; 111: 208-220.	Study design not of interest (animal study)
206	Chen et al.	2022	Glucocorticoid-induced loss of beneficial gut bacterial extracellular vesicles is associated with the pathogenesis of osteonecrosis	Science Advances. 2022; 8:8335.	Study design not of interest (animal study)
207	Chen et al.	2023	Could BMMNCs therapy reduce the mid- and long-term rate of total hip arthroplasty of femoral head necrosis? A systematic review and meta-analysis	Medicine (Baltimore). 2023 28; 102: e34311.	Study design not of interest (review)
208	Chen et al.	2018	Autologous bone marrow mesenchymal stem cell transplantation for the treatment of early femoral head necrosis	Chinese Journal of Tissue Engineering Research. 2018; 22: 4007.	Study design not of interest (animal model)
209	Cheng et al.	2021	METTL14 benefits the mesenchymal stem cells in patients with steroid-associated osteonecrosis of the femoral head by regulating the m6A level of PTPN6	Aging (Albany NY). 2021;13: 25903-25919.	Intervention not of interest (Gene therapy)
210	Rosenblum et al.	2019	Osteonecrosis of the Femoral Head	Orthopedic Clinics of North America. 2019; 50: 139-149.	Study design not of interest (review)
211	Cui et al.	2011	Vascular endothelial cell growth factor combined with bone morphogenetic protein-2-modified bone marrow mesenchymal stem cells in repair of femoral head necrosis	Journal of Clinical Rehabilitative Tissue Engineering Research. 2015; 15: 37-40.	Study design not of interest (Animal model)

212	Cui et al.	2012	Treatment of early osteonecrosis of femoral head with autologous stem cells transplantation by computer navigation	Chinese Journal of Tissue Engineering Research. 2012; 16: 8453.	Study design not of interest (review)
213	Cui et al.	2011	Emerging ideas: Treatment of precollapse osteonecrosis using stem cells and growth factors	Clinical Orthopaedics and Related Research. 2011; 469: 2665-2669.	Study design not of interest (review)
214	Cui et al.	2022	The potential effect of BMSCs with miR-27a in improving steroid-induced osteonecrosis of the femoral head	Scientific Reports. 2022; 12: 21051.	Study design not of interest (in vitro study)
215	Cui et al.	2020	Hypoxic-Mediated Oxidative Stress Condition and Hydroxyapatite-Inducing Osteogenic Differentiation of Human Mesenchymal Stem Cells: A Mathematical Modeling Study	Journal of Biomedical Nanotechnology. 2020; 16: 910-921.	Study design not of interest (mathematical modelling study)
216	Link et al.	2007	MR imaging of therapy-induced changes of bone marrow	European Radiology.2007; 17: 43-61.	Study design not of interest (review)
217	Rojas et al	2018	Outcome of childhood leukaemia survivors and necrosis of the femoral head treated with autologous mesenchymal stem cells	Clinical and Translational Oncology. 2018; 20 :584-590.	Study design not of interest (case reports)
218	Deplano et al.	2014	Bone health in long term survivors of allogeneic bone marrow transplantation	Bone marrow Transplantation. 2014;49: S30-S30.	Study design not of interest (conference paper)
219	Benedetto et al.	2011	Use of bone allografts added with mesenchymal stem cells and growth factors in the treatment of necrosis of femoral head	Journal of orthopaedics and traumatology. 2011;12:S134.	Study design not of interest (Conference presentation)
220	Dilogo et al.	2016	Potency, characteristic, and differentiation of iliac crest bone marrow- derived mesenchymal stem cell of systemic lupus erythematosus patients complicated with	International Journal of PharmTechResearch. 2016; 9:332-339.	Study design not of interest (in vitro study)

			avascular necrosis of femoral head		
221	Diri et al.	2023	Case report: adipose–derived mesenchymal stem cells combined with core decompression in the treatment of early- stage avascular necrosis of the femoral head	International journal of surgery case reports.2023; 102:107861.	Study design not of interest (case report)
222	Edgar et al.	2014	Treatment of avascular necrosis of the femoral head with drilling and injection of concentrated autologous bone marrow	International Orthopedics.2011; 29:218-224.	Study design not of interest (case report)
223	Elalfy et al.	2018	Avascular necrosis of the femoral head in sickle cell disease in Egypt and Oman: A cross-sectional study	Blood. 2018; 132:4921.	Study design not of interest (cross sectional study)
224	Emadedin et al.	2019	Autologous bone marrow–derived CD133 cells with core decompression as a novel treatment method for femoral head osteonecrosis: a pilot study	Cytotherapy.2019.21:107-112	Study design not of interest (quasi experimental study)
225	Etemadi et al.	2023	Glucocorticoid Receptor Polymorphisms and Avascular Osteonecrosis After Kidney Transplantation	Iranian Journal of Kidney disorder. 2023; 1:86-91.	Study design not of interest (retrospective)
226	Froelich et al.	2011	Bisphosphonate-induced osteonecrosis of the external ear canal: A retrospective study	European Archives of oto-rhino-laryngology.2011;268: 1219-1225.	Population not of interest (Bisphosphonate induced ON)
227	Fu et al.	2022	Autologous Stem Cells Combined with Core Decompression on Patients with Osteonecrosis of the Femoral Head	Head.ActaMedica Mediterranea. 2022; 38:2849-2858.	Study design not of interest (not a clinical trial)
228	Fujita et al.	2020	Premature aging syndrome showing random chromosome number instabilities with CDC20 mutation	Aging Cell. 2020; 19: e13251.	Intervention not of interest (Gene therapy)

229	Gagala et al.	2014	The use of osteochondral allograft with bone marrow-derived mesenchymal cells and hinge joint distraction in the treatment of post-collapse stage of osteonecrosis of the femoral head	Medical Hypotheses.2014; 83: 398-400.	Study design not of interest (review)
230	Gangji et al.	2005	Stem cell therapy for osteonecrosis of the femoral head	Expert Opinion on Biological Therapy.2005; 5: 437-442.	Study design not of interest (review)
231	Gangji et al.	2016	Autologous osteoblastic cells versus concentrated bone marrow implantation in osteonecrosis of the femoral head: A randomized controlled single blind study	Annals of the rheumatic diseases.2016; 75:387.	Study design not of interest (Poster presentation)
232	Gao et al.	2018	Ifnb affects osteogenesis-adipogenesis axis in SLE bone marrow	Arthritis Rheumatology. 2018; 70.	Study design not of interest (conference presentation)
233	Gómez et al.	2015	Cell therapy with CD34/CD133 enriched in avascular necrosis of femoral head	Bone Marrow Transplantation. 2015;50:S317-S317	Study design not of interest
234	Barrena et al	2021	Implantation of autologous expanded mesenchymal stromal cells in hip osteonecrosis through percutaneous forage: Evaluation of the operative technique	Journal of Clinical Medicine. 2021; 10:743.	Outcome not of interest (operative technique)
235	Goodman et al.	2015	Treatment of Secondary Osteonecrosis of the Knee with Local Debridement and Osteoprogenitor Cell Grafting	Journal of Arthroplasty. 2015; 30: 18926.	Study design not of interest (Case series)
236	Grayson et al.	2015	Stromal cells and stem cells in clinical bone regeneration	Nature Reviews Endocrinol. 2015; 11:140-150.	Study design not of interest (review)
237	Gupta et al.	2022	Biology of Bone Morphogenetic Proteins in Skeleton Disease: Osteonecrosis in Sickle	Current Protein & Peptide Science.2022; 23:264-270.	Study design not of interest (review)

			Cell Disease Patients		
238	Han et al.	2020	Knockdown of POSTN Inhibits Osteogenic Differentiation of Mesenchymal Stem Cells from Patients with Steroid-Induced Osteonecrosis	Frontiers in Cell and Developmental Biology. 2020; 8:606289.	Study design not of interest (in vitro study)
239	Hauzeur et al.	2010	Phases 1-3 clinical trials using adult stem cells in osteonecrosis and Non-union fractures	Stem Cells International. 2010; 2010:1-4.	Study design not of interest (review)
240	Hauzeur et al.	2008	Cell-based therapy in bone diseases	Revue Medicale de Liege.2008;63:20-25	Study design not of interest (cohort study)
241	He et al.	2016	Comparison of core decompression with stem cell transplantation and tantalum rod implanting in treating stage II non-traumatic osteonecrosis of femoral head	Zhongguo Gu Shang.2016; 29:1119-1124.	Study design not of interest (cohort study)
242	Hernigou et al.	2021	Cell therapy for post-traumatic hip osteonecrosis in young patients	Morphologie.2021;105:127-133.	Study design not of interest (retrospective case control analysis)
243	Hernigou et al.	2002	Treatment of osteonecrosis with autologous bone marrow grafting	Clinical Orthopedics and Related Research. 2002; 405:14-23.	Study design not of interest (Cohort study)
244	Hernigou et al.	2018	Stem cell therapy in early post-traumatic talus osteonecrosis	International Orthopedics. 2018; 42:2949-2956.	Study design not of interest (Cohort study)
245	Hernigou et al.	2017	Allografts supercharged with bone-marrow-derived mesenchymal stem cells possess equivalent osteogenic capacity to that of autograft: a study with long-term follow-ups of human biopsies	International Orthopedics. 2017; 41:127-132.	Study design not of interest (Cohort study)
246	Hernigou et al.	2014	Osteonecrosis repair with bone marrow cell therapies: State of the	Bone.2015; 70:102-109.	Study design not of interest (review)

			clinical art		
247	Hernigou et al.	2004	Core decompression with marrow stem cells	Operative Techniques in Orthopaedics. 2004; 14:68-74.	Study design not of interest (case report)
248	Hernigou et al.	2005	The use of percutaneous autologous bone marrow transplantation in Non-union and avascular necrosis of bone	Journal of Bone and Joint Surgery. 2005; 87:896-902.	Study design not of interest (review)
249	Hernigou et al.	2016	Stem cell therapy for the treatment of hip osteonecrosis: A 30-year review of progress	Clinical Orthopedics Surgery. 2016; 8:1-8.	Study design not of interest (review)
250	Hernigou et al.	2019	Cellular Therapy for the Treatment of Osteonecrosis: From Bench to Bedside	Instructional course lectures.2020;69 :139-148.	study design not of interest (review)
251	Hernigou et al.	2008	Bone marrow injection in hip osteonecrosis	Techniques in Orthopaedics.20 08; 23:18-25	Study design not of interest (review)
252	Homma et al.	2014	Supercharging allografts with mesenchymal stem cells in the operating room during hip revision	International Orthopedics. 2014 38:2033-2044.	Study design not of interest (cohort study)
253	Houdek et al.	2018	Stem Cells Combined with Platelet-rich Plasma Effectively Treat Corticosteroid-induced Osteonecrosis of the Hip: A Prospective Study	Clinical Orthopedic Related Research. 2018; 476:388-397.	Study design not of interest (case series)
254	Hu et al.	2014	Treatment of early osteonecrosis of the femoral head with debridement, bone grafting and bone marrow mononuclear cells transplantation: Functional evaluation of the hip joint	Modern rehabilitation.20 14; 24:197-202.	Study design not of interest (Case analysis)
255	Huang et al.	2021	Steroid-Induced Osteonecrosis of the Femoral Head: Novel Insight into the Roles of Bone Endothelial Cells in Pathogenesis and Treatment	Frontiers in Cell and Developmental Biology. 2021; 9: 777697.	Study design not of interest (review)

256	Huang et al.	2022	Borderline Developmental Dysplasia of the Hip: A Risk Factor Predicting the Development and Poor Prognosis after Core Decompression for Idiopathic Osteonecrosis of the Femoral Head	OrthopedicSurgery. 2022; 14:2427-2435.	Study design not of interest (retrospective study)
257	Huang et al.	2018	High levels of GSK-3β signalling reduce osteogenic differentiation of stem cells in osteonecrosis of femoral head	Journal of Biochemistry. 2018; 163:243-251.	Outcomes not of interest (mechanism regulating MSC)
258	Ilas et al.	2020	The osteogenic commitment of CD271+CD56+ bone marrow stromal cells (BMSCs) in osteoarthritic femoral head bone	Scientific Reports. 2020; 10:11145.	Study design not of interest (in vivo study)
259	Im et al.	2015	Stem Cells for Reutilization in Bone Regeneration	Journal of Cellular Biochemistry. 2015; 116: 487-493.	Study design not of interest (review)
260	Im et al.	2023	Regenerative medicine for osteonecrosis of the femoral head	Bone Joint Research. 2023; 12:5-8.	Study design not of interest (review)
261	Ji et al.	2008	Three-tunnels core decompression with implantation of bone marrow stromal cells (bMSCs) and decalcified bone matrix (DBM) for the treatment of early femoral head necrosis	Zhongguo Gu Shang. 2008; 21:776-778.	Study design not of interest (Retrospective study)
262	Jia et al.	2015	Bone, tissue and cell transplantation for fractures of the femoral neck and femoral shaft	Journal of Tissue Engineering Research. 2015, (21): 3424-3428.	Study design not of interest (retrospective study)
263	Kahn et al.	2021	Late effects after allogeneic hematopoietic cell transplantation among children and adolescents with non- malignant disorders: A report from the center for international blood and	Blood.2021;138 :412.	Study design not of interest (retrospective study)

			marrow transplant research (CIBMTR)		
264	Kang et al.	2019	Clinical efficiency of bone marrow mesenchymal stem cell implantation for osteonecrosis of the femoral head: a matched pair control study with simple core decompression	Stem cell research and therapy.2018;9:274	Study design not of interest (review)
265	Kato et al.	2018	Elevated Expression of Dkk-1 by Glucocorticoid Treatment Impairs Bone Regenerative Capacity of Adipose Tissue-Derived Mesenchymal Stem Cells	Stem Cells and Development. 2018;27:85-99.	Study design not of interest (in vitro study)
266	Khan et al.	2021	Autologous stem cell implantation with core decompression for avascular necrosis of the femoral head using a new device	Annals of the Royal College of Surgeons of England. 2021; 103: 508-513.	Study design not of interest (retrospective review)
267	Kumagai et al.	2018	Quantitative assessment of mesenchymal stem cells contained in concentrated autologous bone marrow aspirate transplantation for the treatment of osteonecrosis of the femoral head: predictive factors and differences by etiology	BioMed Central Research Notes. 2018; 11:848.	Study design not of interest (Observational cohort study)
268	Kuroda et al.	2016	A pilot study of regenerative therapy using controlled release of recombinant human fibroblast growth factor for patients with pre-collapse osteonecrosis of the femoral head	International Orthopaedics. 2016; 40:1747-1754.	Intervention not of interest (Gene therapy)
269	Kuroda et al.	2020	Recombinant human FGF-2 therapy for osteonecrosis of the femoral head: 5-year follow-up	Regenerative Medicine. 2020; 15:2261-2271.	Intervention not of interest (Gene therapy)
270	Kuroda et al.	2021	Percutaneous autologous impaction bone graft for advanced femoral head	Journal of Orthopaedic Surgery and	Study design not of interest (retrospective

			osteonecrosis: a retrospective observational study of unsatisfactory short-term outcomes	Research. 2021;16:141.	study)
271	Kuroda et al.	2021	Recombinant human FGF-2 for the treatment of early-stage osteonecrosis of the femoral head: TRION, a single-arm, multicenter, Phase II trial	Regenerative Medicine. 2021; 16:535-548.	Intervention not of interest (Gene therapy)
272	Kuroyanagi et al.	2017	Interleukin-6 inhibits osteoblastic differentiation of bone marrow stromal cells and decreases bone formation following ischemic osteonecrosis in adolescent mice	Journal Of Bone And Mineral Research.2017; S341-S342.	Study design not of interest (Animal model)
273	Lacza et al.	2012	Cell therapy without exogenous stem cells: Insights from human experiments using serum-augmented bone grafts	In Journal Of Tissue Engineering And Regenerative Medicine. 2012; 6:400-401.	Study design not of interest (Review)
274	Landgraeber et al.	2013	Advanced core decompression, a new treatment option of avascular necrosis of the femoral head-a first follow-up	Journal of Tissue Engineering and Regenerative Medicine. 2013; 7: 893-900.	Intervention not of interest (No stem cell intervention)
275	Lei et al.	2010	Extracorporeal shock wave effects on osteogenic differentiation of bone marrow mesenchymal stem cells at the non-necrotic area of patients with steroid- induced avascular necrosis of the femoral head	Chinese Journal of Tissue Engineering Research.2010; 14: 3446-3450.	Study design not of interest (in vitro study)
276	Li et al.	2020	Identification of long non-coding RNAs expressed during the osteogenic differentiation of human bone marrow-derived mesenchymal stem cells obtained from patients with ONFH	International Journal of Molecular Medicine. 2020;46:1721-1732.	Intervention not of interest (Gene therapy)

277	Li et al.	2014	Avascular necrosis of bone after allogeneic hematopoietic cell transplantation in children and adolescents	Biology of Blood and Marrow Transplant. 2014; 20:587-592.	Study design not of interest (case control study)
278	Li et al.	2023	Review of the Pathogenesis, Diagnosis, and Management of Osteoradionecrosis of the Femoral Head	Medical Science Monitor. 2023; 29:e940264.	Study design not of interest (review)
279	Liang et al.	2023	Clinical outcomes of autologous platelet-rich plasma and bone marrow mononuclear cells grafting combined with core decompression for Association Research Circulation Osseous II–IIIA stage non-traumatic osteonecrosis of the femoral head	International Orthopaedics 2023; 47:2181-2188.	Study design not of interest (Retrospective study)
280	Liu et al.	2019	An exploratory study of articular cartilage and subchondral bone reconstruction with bone marrow mesenchymal stem cells combined with porous tantalum/Bio- Gide collagen membrane in osteonecrosis of the femoral head	Materials Science & Engineering C. 2019; 99:1123-1132.	Study design not of interest (in vitro study)
281	Liu et al.	2019	Core decompression combined with bone marrow mesenchymal stem cell transplantation for treating osteonecrosis of the femoral head	International Journal of Surgery. 2019; 69:23-31.	Study design (Case analysis)
282	Liu et al.	2018	Investigating clinical failure of core decompression with autologous bone marrow mononuclear cells grafting for the treatment of non-traumatic osteonecrosis of the femoral head	International Orthopaedics. 2018; 42:1575-1583.	Study design not of interest (cohort study)
283	Lu et al.	2010	Late effects of haematopoietic stem cell transplantation in	Journal of Cardiovascular Magnetic	Population not of interest (different disease)

			children	Resonance. 2019; 21:6.	
284	Ma et al.	2021	Core Decompression with Local Administration of Zoledronate and Enriched Bone Marrow Mononuclear Cells for Treatment of Non - Traumatic Osteonecrosis of Femoral Head	Orthopaedic Surgery. 2021; 13 :1843-1852.	Study design not of interest (retrospective study)
285	Man et al.	2007	Human umbilical cord blood-derived mesenchymal stem cells via intravenous infusion for treatment of alcoholic osteonecrosis of the femoral head	ZhongguoZuzhiGongchengYanjiuyuLinchuangKangfu. 2007; 11:4734.	Study design not of interest (cohort study)
286	Mao et al.	2013	The efficacy of targeted intraarterial delivery of concentrated autologous bone marrow containing mononuclear cells in the treatment of osteonecrosis of the femoral head: A five-year follow-up study	Bone. 2013; 57:509-516.	Study design not of interest (cohort study)
287	Campbell et al.	2014	Markedly increased mesenchymal stem cell activity in MRI bone marrow lesions compared with non-involved bone in osteoarthritic hips	Arthritis & Rheumatology. 2014; 66: S446-S447	Population is not of interest (Different disease, Osteoarthritis)
288	Martin et al.	2013	Use of concentrated bone marrow aspirate and platelet rich plasma during minimally invasive decompression of the femoral head in the treatment of osteonecrosis	Croatian Medical Journal. 2013; 54:219-224.	Study design not of interest (retrospective review)
289	Martišova et al.	2016	Avascular necrosis of bone in adult patients surviving more than 2 years after allogeneic stem cell transplantation in years 2001-2012-experience of Slovak transplantation centre	Inhaematologica. 2016; 101: 858-858.	Study design not of interest (Review)

290	Maruyama et al.	2019	Cell-Based and Scaffold-Based Therapies for Joint Preservation in Early-Stage Osteonecrosis of the Femoral Head	Journal of bone and joint surgery Reviews. 2019; 7: e5	Study design not of interest (review)
291	Mathieu et al.	2013	Study of mesenchymal stem cells and endothelial progenitor cells in osteonecrosis of the femoral head	Not Available	Full text and abstract not available
292	Melero et al.	2014	Avascular necrosis after allogeneic transplantation hematopoietic progenitors: Single-center experience	Inbone Marrow Transplantation. 2014; 49: S275-S275	Study design not of interest (conference presentation)
293	Loingsigh et al.	2010	A comparison of avascular necrosis incidence in patients with acute lymphoblastic leukaemia treated by transplantation versus chemotherapy	Inbone Marrow Transplantation 2010; 45: S103-S103.	Study design not of interest (Conference presentation)
294	Nöth et al.	2007	Cell based therapy for the treatment of femoral head necrosis	Die Orthopädie. 2007; 36:466-471.	Study design not of interest (review)
295	Ouederni et al.	2023	Incidence and risk factors for osteonecrosis of the femoral head in five hundred and ten sickle cell disease paediatric patients	International Orthopaedics. 2023; 47:2941-2952.	Study design not of interest (retrospective study)
296	Pak et al.	2011	Regeneration of human bones in hip osteonecrosis and human cartilage in knee osteoarthritis with autologous adipose-tissue-derived stem cells: A case series	Journal of Medical Case Reports. 2011; 5:296.	Study design not of interest (case series)
297	Pan et al.	2020	Prognosis after autologous peripheral blood stem cell transplantation for osteonecrosis of the femoral head in the pre-collapse stage: A retrospective cohort study	Stem Cell Research & Therapy 2020; 11:83.	Study design not of interest (Retrospective cohort study)

298	Poggio et al.	2006	Surgical treatment for vascular necrosis of femoral head after hematopoietic stem cell transplantation	Medicina clínica. 2006;127:738-740.	Study design not of interest (Retrospective cohort study)
299	Talathi et al.	2018	Autologous stem cell implantation with core decompression for avascular necrosis of the femoral head	Journal of Clinical Orthopaedics& Trauma. 2018; 9:349-352.	Study design not of interest (retrospective review)
300	Tauchmano và et al.	2003	Avascular necrosis in long-term survivors after allogeneic or autologous stem cell transplantation: A single center experience and a review	Cancer. 2003;97:2453-2461.	Study design not of interest (Review)
301	Tong et al.	2014	Treatment of Non - traumatic femoral head avascular necrosis by perfusion of bone marrow stromal stem cells through optional artery	Zhongguo Gu Shang. 2014; 27 :565-569.	Study design not of interest (Cohort study)
302	Velkovski et al.	2023	Analysis of Results After Surgical Application of Bone Marrow Aspirate Stem Cell Concentrate in the Treatment of Avascular Necrosis of the Femoral Head	PRILOZI. 2023; 44:79-87.	Study design not of interest (prospective cohort study)
303	Wang et al.	2015	Autologous peripheral blood mononuclear cell transplantation with porous core decompression for treatment of avascular necrosis of the femoral head: An 11-month follow-up evaluation	Chinese Journal of Tissue Engineering Research, 2015, 19: 114-118.	Study design not of interest (Case analysis)
304	Wang et al.	2023	Comparison of current treatment strategy for osteonecrosis of the femoral head from the perspective of cell therapy	Frontiers in Cell and Developmental Biology. 2023; 11:995816.	Study design not of interest (review)
305	Wang et al.	2018	Autologous iliac bone graft mixed with blood stem cells for early femoral head osteonecrosis	Journal of Biomaterials and Tissue Engineering. 2018;8 :1505-	Study design not of interest (cohort study)

				1511.	
306	Wang et al.	2008	Stem cell transplantation for middle and late stages of femoral head necrosis	Stem Cells Cloning. 2014; 7:65-70.	Study design not of interest (cohort study)
307	Xu et al.	2008	Arthroscopic debridement and medullary core decompression combined with autologous peripheral blood stem cell transplantation in the treatment of early avascular necrosis of the femoral head in 38 cases	ZhongguoZuzhiGongchengYanjiu Yu LinchuangKangfu. 2008; 12 :515.	Study design not of interest (cohort study)
308	Yamasaki et al.	2010	Bone-marrow-derived mononuclear cells with a porous hydroxyapatite scaffold for the treatment of osteonecrosis of the femoral head: A preliminary study	The Journal of Bone and Joint Surgery. 2010; 92 :337-341.	Study design not of interest (Preliminary retrospective study)
309	Yan et al.	2015	Autologous mesenchymal stem cell implantation in the management of osteonecrosis of the femoral head	Current Orthopaedic Practice. 2015; 26 :265-268.	Study design not of interest (Retrospective study)
310	Yang et al.	2007	Clinical study on the improvement of ischemia condition with stem cell transplantation in 122 cases necrosis of femoral head	Zhonghua Wai Ke Za Zhi. 2007; 45:1428-1431.	Study design (case series)
311	Yang et al.	2006	Effect of bone marrow stem cell transplantation via artery on femoral head necrosis in 63 cases	Not Available	Study design (case series)
312	Yu et al.	2008	Autologous peripheral blood stem cell transplantation for the treatment of avascular necrosis of the femoral head in 21 cases	Chinese Journal of Tissue Engineering Research. 2014;18 :8174.	Study design not of interest (retrospective study)
313	Zhang et al.	2020	Changes in serum levels of fibroblast growth factor-2, hypoxia-inducible factor-1alpha and vascular endothelial growth factor in patients with avascular necrosis of	Chinese Journal of Tissue Engineering Research. 2020; 24:14.	Study design not of interest (cohort study)

			femoral head treated by enriched autologous bone marrow stem cell transplantation combined with core decompression		
314	Zhang et al.	2015	Bone marrow mesenchymal stem cell transplantation combined with core decompression and bone grafting in the repair of osteonecrosis of femoral head	Chinese Journal of Tissue Engineering Research. 2015; 19: 883-890.	Study design not of interest (Cohort study)
315	Zheng et al.	2013	Autologous iliac crest grafting combined with stem cells transplantation in the treatment of early osteonecrosis of the femoral head	Chinese Journal of Tissue Engineering Research. 2013; 17: 4363-4370.	Study design not of interest (Cohort study)
316	Liu et al.	2009	Treatment for osteonecrosis of femoral head by hVEGF-165 gene modified marrow stromal stem cells under arthroscope	Zhonghua Yi Xue Za Zhi. 2009;89 :2629-2633.	Intervention not of interest (Gene therapy)
317	Richard et al.	2021	Outcomes of free vascularized fibular graft for post-traumatic osteonecrosis of the femoral head	Injury. 2021; 52 :3653-3659.	Study design not of interest (Retrospective analysis)
318	Chen et al.	2022	Glucocorticoid-induced loss of beneficial gut bacterial extracellular vesicles is associated with the pathogenesis of osteonecrosis	Science Advances. 2022;8: 8335.	Study design not of interest (Animal study)
319	Pak et al.	2021	Endoscopic observation finding in the core decompression procedure of osteonecrosis of femoral head and effect of additional treatments	International Orthopaedics. 2021;45: 95-99.	Study design not of interest (Cohort study)
320	Sun et al.	2016	Focused extracorporeal shock wave for osteonecrosis of the femoral head with leukaemia after allo-HSCT: a case series	Bone Marrow Transplantation. 2016; 51 :1507-1509.	Study design not of interest (Letter to the editor)

321	Torri et al.	2001	Osteonecrosis of the femoral head after allogeneic bone marrow transplantation	Clinical Orthopaedics and Related Research. 2001; 382:124-132.	Study design not of interest (Retrospective analysis)
322	Kawate et al.	2006	Tissue-engineered approach for the treatment of steroid-induced osteonecrosis of the femoral head: transplantation of autologous mesenchymal stem cells cultured with beta-tricalcium phosphate ceramics and free vascularized fibula	Artificial Organs. 2006; 30:960-962.	Study design not of interest (Case series)
323	Jones et al.	2008	Cell-based therapies for osteonecrosis of the femoral head	Biology of Blood and Marrow Transplantation. 2008; 14:1081-1087.	Study design not of interest (Review)
324	Hernigou et al.	2018	Cell therapy versus simultaneous contralateral decompression in symptomatic corticosteroid osteonecrosis: a thirty-year follow-up prospective randomized study of one hundred and twenty-five adult patients	International Orthopaedics (SICOT) 42, 1639–1649 (2018)	Outcome given at 25 years follow up
325	Gangji et al.	2011	Autologous bone marrow cell implantation in the treatment of non-traumatic osteonecrosis of the femoral head: Five-year follow-up of a prospective controlled study	Bone. 2011 Nov; 49(5):1005-9	Study design (Randomisation is not present)
326	Ayoyama et al.	2014	An exploratory clinical trial for idiopathic osteonecrosis of femoral head by cultured autologous multipotent mesenchymal stromal cells augmented with vascularized bone grafts	Tissue Eng Part B Rev. 2014 Aug; 20(4):233-42.	Study design (CCT, Randomisation is not present)

327	Cai et al.	2014	Cotransplantation of bone marrow mononuclear cells and umbilical cord mesenchymal stem cells in avascular necrosis of the femoral head	Transplant Proc. 2014 Jan-Feb; 46(1):151-5.	Study design (CCT, Randomisation is not present)
328	Zhao et al.	2015	Autologous bone marrow mesenchymal stem cells associated with tantalum rod implantation and vascularized iliac grafting for the treatment of end-stage osteonecrosis of the femoral head.	Biomed Res Int. 2015; 2015:240506.	Study design (CCT, Randomisation is not present)
329	Chen et al.	2016	efficacy of umbilical cord-derived mesenchymal stem cell-based therapy for osteonecrosis of the femoral head: A three-year follow-up study	Mol Med Rep. 2016 Nov; 14(5):4209-4215.	Study design (CCT, Randomisation is not present)
330	Wu et al.	2020	Correlation between the efficacy of stem cell therapy for osteonecrosis of the femoral head and cell viability	MC MusculoskeletDisord. 2020 Jan 29; 21(1):55.	Study design (CCT, Randomisation is not present)
331	Barrena et al.	2021	Osteonecrosis of the Femoral Head Safely Healed with Autologous, Expanded, Bone Marrow-Derived Mesenchymal Stromal Cells in a Multicentric Trial with Minimum5 Years Follow-Up	J Clin Med. 2021 Feb 1; 10(3):508.	Study design (CCT, Randomisation is not present)
332	Yoon et al.	2021	Culture-Expanded Autologous AdiposeDerived Mesenchymal Stem Cell Treatment for Osteonecrosis of the Femoral Head	Clin Orthop Surg. 2021 Mar;13(1):37-46	Study design (CCT, Randomisation is not present)
333	Sugaya et al.	2022	An exploratory clinical trial for concentrated autologous bone marrow aspirate transplantation in the treatment of osteonecrosis of the femoral head	Eur J Orthop Surg Traumatol. 2023 Feb; 33(2):441-447.	Study design (CCT, Randomisation is not present)

334	Blanco et al.	2023	Long-Term Results of a Phase I/II Clinical Trial of Autologous Mesenchymal Stem Cell Therapy for Femoral Head Osteonecrosis	J Clin Med. 2023 Mar 8; 12(6):2117.	Study design (CCT, Randomisation is not present)
336	Hernigou et al.	2018	Subchondral stem cell therapy versus contralateral total knee arthroplasty for osteoarthritis following secondary osteonecrosis of the knee	Int Orthop. 2018; 42(11):2563-2571.	Population not of interest (ONK)
337	Hernigou et al.	2021	Mesenchymal stem cell therapy improved outcome of early post-traumatic shoulder osteonecrosis: a prospective randomized clinical study of fifty patients with over ten-year follow-up	Int Orthop. 2021;45(10):2643-2652	Population not of interest (ONHH)

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3. CARTILAGE DEFECTS

i. **Key question in PICO format**

ii. **Search strategy**

iii. **PRISMA flow diagram**

iv. **Summary of included studies**

v. **Classification of studies based on level of stem cell manipulation**

vi. **Evidence to decision framework**

vii. **Data extraction**

viii. **List of excluded studies**

i. Key question in PICO format:

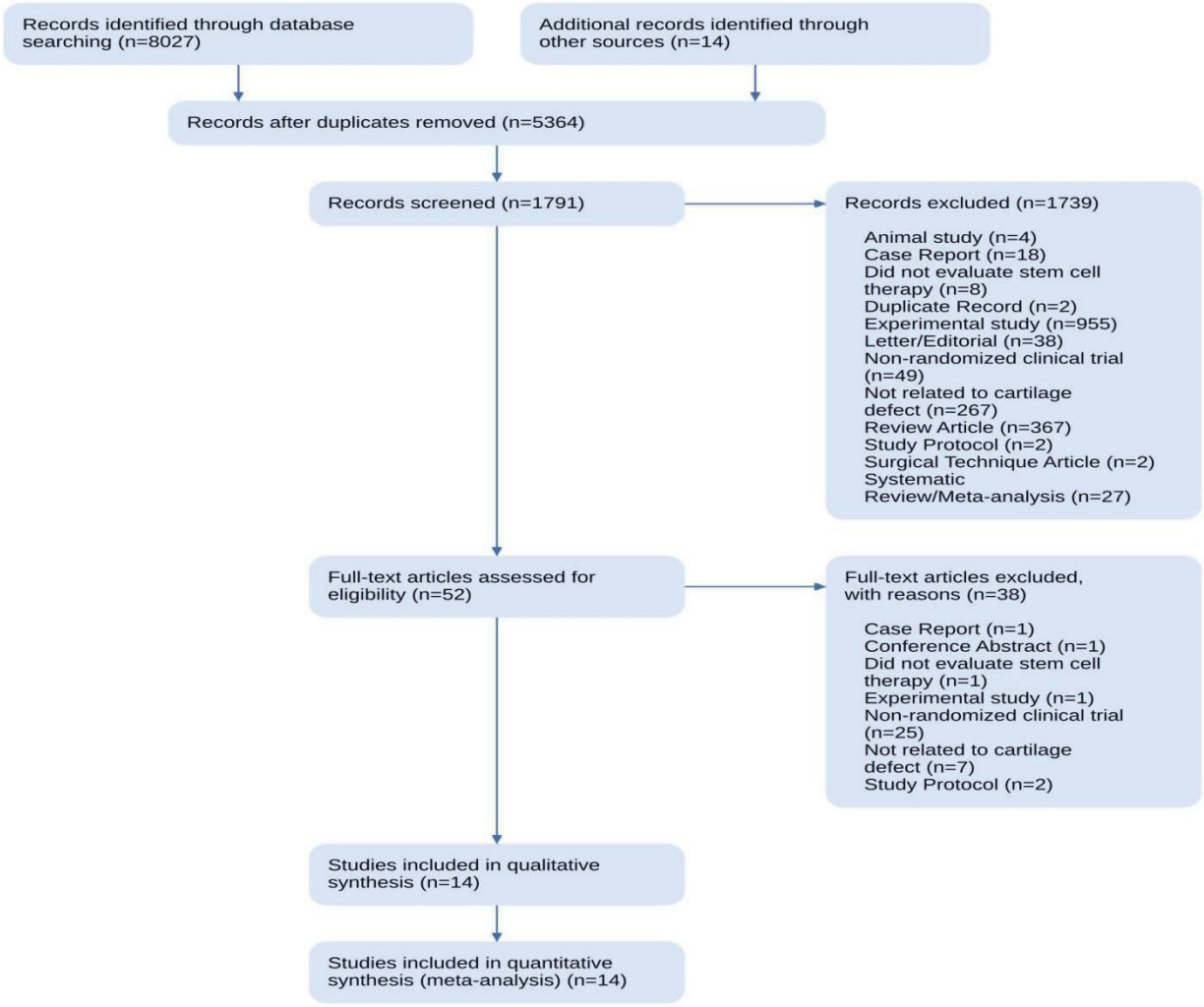
Population: Patients with cartilage defects
Intervention: Any Stem cell and product derived from stem cells
Comparator: Usual Care/ Conventional Care
Critical Outcomes: Efficacy: Reduction in pain, Disability; Safety: Severe Adverse Events

ii. Search strategy:

Search	Database	Query	Date	Results
1	PubMed	((((osteochondral defect) OR (osteochondral lesion)) OR (cartilage defect)) OR (osteochondritis dissecans)) AND (((((((((stem cell) OR (induced pluripotent stem cell)) OR (hematopoietic stem cell)) OR (embryonic stem cell)) OR (adipocyte derived stem cell)) OR (bone marrow derived stem cell)) OR (bone marrow aspirate concentrate)) OR (stromal vascular fraction)) AND (((therapy) OR (repair)) OR (regeneration)))	Oct 23, 2023	2605
2	Embase	('osteochondral defect'/exp OR 'osteochondral defect' OR 'osteochondral lesion' OR 'cartilage defect' OR 'osteochondritis dissecans') AND ('stem cell' OR 'embryonic stem cell' OR 'hematopoietic stem cell' OR 'adipocyte derived stem cell' OR 'bone marrow derived stem cell' OR 'induced pluripotent stem cell' OR 'bone marrow aspirate concentrate' OR 'stromal vascular fraction') AND ('therapy' OR 'repair' OR 'regeneration')	Oct 23, 2023	1048
3	Web of Science	#1 (((ALL=(osteochondral defect)) OR ALL=(osteochondral lesion)) OR ALL=(cartilage defect)) OR ALL=(osteochondritis dissecans) #2 (((((((ALL=(stem cell)) OR ALL=(induced pluripotent stem cell)) OR ALL=(embryonic stem cell)) OR ALL=(hematopoietic stem cell)) OR ALL=(adipocyte derived stem cell)) OR ALL=(bone marrow derived stem cell)) OR ALL=(bone marrow aspirate concentrate)) OR ALL=(stromal vascular fraction) # 3((ALL=(therapy)) OR ALL=(repair)) OR ALL=(regeneration) #4 #2 AND #3 #5 #1 AND #4	Oct 23, 2023	4340

4	COCHRANE CENTRAL	ID Search Hits #1 OSTEOCHONDRAL DEFECT 57 #2 CARTILAGE DEFECT 294 #3 OSTEOCHONDRAL LESION 71 #4 OSTEOCHONDRITIS DISSECANS 61 #5 #1 OR #2 OR #3 OR #4 387 #6 STEM CELL 15199 #7 INDUCED PLURIPOTENT STEM CELL 68 #8 EMBRYONIC STEM CELL 84 #9 HEMATOPOIETIC STEM CELL 5963 #10 ADIPOCYTE DERIVED STEM CELL 15 #11 BONE MARROW DERIVED STEM CELL 872 #12 BONE MARROW ASPIRATE CONCENTRATE 112 #13 STROMAL VASCULAR FRACTION 196 #14 #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 15380 #15 THERAPY 846834 #16 REPAIR 20967 #17 REGENERATION 5669 #18 #15 OR #16 OR #17 862910 #19 #14 AND #18 10943 #20 #5 AND #19 37	Oct 23, 2023	34
6	Other Sources	Meng etl al. Adipose Tissue-Derived Mesenchymal Stem Cells as a Potential Restorative Treatment for Cartilage Defects: A PRISMA Review and Meta-Analysis	Nov 16, 2023	5
7	Other Sources	Kim et al. Intra-articular injection of mesenchymal stem cells for clinical outcomes and cartilage repair in osteoarthritis of the knee: a metaanalysis of randomized controlled trials	Nov 16, 2023	9
Total				**8041**

iii. PRISMA flow diagram:



iv. Summary of included studies:

Study	Population	Intervention	Comparison	Outcomes	Comments
Wong et al. 2013[1]	Knee – FCD +OA	HTO+MicroFx+Postop BMDSC & HA	HTO+MicroFx+Postop HA	• IKDC • Tegner • Lysholm • MOCART	-
Akgun et al. 2015[2]	Knee – FCD	SDSC+Collagen Matrix	mACI	• VAS • KOOS • Tegner	-
Koh et al. 2016[3]	Knee – FCD	ADMSC+fibrin+MicroFx	MicroFx	• VAS • KOOS • Lysholm	-
Hong et al. 2019[4]	Knee – OA	SVF	HA	• VAS • WOMAC • MOCART • WORMS	Excluded, because stem cell characterization was not performed
Lee et al. 2019[5]	Knee – OA	ADMSC	Saline	• VAS • KOOS • WOMAC	-
Hashimoto et al. 2019[6]	Knee – FCD + OA	BMDSC+MicroFx	MicroFx	• IKDC • KOOS • MOCART	-
Lim et al. 2021[7]	Knee – FCD + OA	UCB-MSC+HA+MicroFx	MicroFx	• VAS • IKDC • WOMAC • ICRS Grade of Improvement • ICRS Histological Score	-
Saw et al. 2021[8]	Knee -FCD	MicroFx+ Postop PBSC + HA	HA	• IKDC • KOOS • NRS	-
Liu et al. 2021[9]	Knee – FCD	BMDSC+Kartigen	MicroFx	• VAS	-

				• IKDC	
Kim et al. 2022[10]	Knee – OA	HTO+Postop ADMSC	HTO	• KOOS • WOMAC • ICRS • MOCART	-
Venosa et al. 2022[11]	Knee – FCD	ADMSC+PRP+MicroFx	MicroFx+PRP	• VAS • IKDC • KOOS • SF12	Excluded, because stem cell characterization was not performed
de Girolamo et al. 2019[12]	Knee – FCD	BMDSC+mACI	mACI	• KOOS • Lysholm	-
Saw et al. 2013[13]	Knee – FCD	MicroFx+Postp PBSC & HA	MicroFx+Postop HA	• IKDC • ICRS II	-
Zhou et al. 2021[14]	Knee – FCD	ADMSC+Arhroscopy	Arthroscopy	• VAS • WOMAC • MOCART	-

v. Classification of studies on the basis of level of manipulation of the stem cell/ Stem cell derived product used (*interpreted by the Secretariat as defined by CDSCO* and the information provided in the trial itself*):

S. No.	Trial Details	Intervention	Level of manipulation	Information extracted from trial
1.	Wong et al. 2013	Autologous MSCs	More	*"Autologous MSCs were cultured from bone marrow in a class B clean room environment."*
2.	Koh et al. 2016	Adipose Derived MSCs	Less	*"We collected subcutaneous adipose tissue from the patient's buttock and isolated the stromal vascular fraction and MSCs by centrifugation."*
3.	Lee et al. 2019	Autologous Adipose Derived MSC	More	*"AD-MSCs (Jointstem; R-Bio, Seoul, Korea) used in the current study were isolated and cultured"*
4.	Hashimoto et al. 2019	Autologous Bone Marrow Derived MSCs.	More	*"Cell culture was performed at the cell processing centers."*

5.	Lim et al. 2021	Allogeneic Umbilical Cord Blood–Derived Mesenchymal Stem Cell	More	*"Allogeneic UCB-MSCs were produced at a cell manufacturing facility operated by MEDIPOST Co Ltd, in full compliance with the Good Manufacturing Practice requirements…. The ex vivo culture-expansion manufacturing process of the UCB MSCs is a scaled adaptation of the technique described by Yang et al and involves initial isolation steps to remove hematopoietic elements, followed by MSC expansion of the nucleated cells in culture medium (alpha-Minimal Essential Medium; Gibco BRL) supplemented with 10% fetal bovine serum."*
6.	Saw et al. 2021	Peripheral Blood Stem Cells	Less	*"Autologous PBPCs were collected by an automated cell separator (apheresis) by central venous access. Venous access was achieved through a femoral double-lumen catheter placed into the contralateral leg, under ultrasound guidance, performed by a consultant radiologist. Apheresis was performed by use of the Spectra Optia Apheresis Machine (Caridian BCT, Denver, CO). A fresh aliquot of 8 mL of PBPCs was separated for fresh intra-articular injection into the operated knee. The remaining PBPCs were cryopreserved in 10% dimethyl sulfoxide and divided into 4-mL cryovials for storage in liquid nitrogen at –196°C. Flow cytometry with $CD34^{+}$ (hematopoietic stem cells) and CD105+ (markers for mesenchymal stem cells) was quantified. Flow cytometry was performed with a Beckman Coulter FC500 device (Beckman Coulter, Fullerton, CA)."*
7.	Liu et al. 2021	Kartigen (a matrix with autologous bone marrow mesenchymal stem cell-derived chondrocyte precursors)	More	*"Cell culture was performed under standard operative procedures at the cell processing unit (CPU) of Kartigen Biomedical Inc. (Taipei, Taiwan), following the Good Tissue Practice regulations."*
8.	Kim et al. 2022	Adipose Derived MSCs	More	*"ADMSCs were isolated from abdominal subcutaneous fat by lipoaspiration and cultured under Good Manufacturing Practices conditions"*
9.	De Girolamo et al. 2019	Concentrated bone marrow aspirate	Less	*"Bone marrow was collected by multiple localizations (about 4–5 mL per sampling) to avoid the peripheral blood dilution effect [22,23]; the samples were then centrifuged at 3200 rpm for 15 min (room*

				temperature) at the point of care using the MarrowStimTM device (Biomet, USA, currently named "BioCue", Zimmer-Biomet, Warsaw, IN, USA) according to the manufacturer's instructions. At the end of the centrifugation a phase enriched in mononuclear cells, including mesenchymal progenitors, was obtained."
10.	Saw et al. 2013	Autologous Peripheral Blood Stem Cells (PBSCs)	Less	*"Autologous PBPCs were collected by an automated cell separator (apheresis) by central venous access. Venous access was achieved through a femoral double-lumen catheter placed into the contralateral leg, under ultrasound guidance, performed by a consultant radiologist. Apheresis was performed by use of the Spectra Optia Apheresis Machine (Caridian BCT, Denver, CO). A fresh aliquot of 8 mL of PBPCs was separated for fresh intra-articular injection into the operated knee. The remaining PBPCs were cryopreserved in 10% dimethyl sulfoxide and divided into 4-mL cryovials for storage in liquid nitrogen at –196°C. Flow cytometry with $CD34^{+}$ (hematopoietic stem cells) and CD105+ (markers for mesenchymal stem cells) was quantified. Flow cytometry was performed with a Beckman Coulter FC500 device (Beckman Coulter, Fullerton, CA)."*
11.	Akgun et al. 2015	Matrix-induced autologous mesenchymal stem cell implantation	More	*"For MSCs, the digested material was centrifuged at 1,000 rpm for 10 min, and the pellet was cultured in high glucose Dulbecco's Modified Eagle's Medium (DMEM; Gibco BRL, Life Technologies Inc., Rockville, MD, USA) containing 1 % penicillin/streptomycin (Gibco BRL) and 10 % autologous serum. Cell growth proceeded for 1 week; MSCs were then harvested using a 0.25 % trypsin solution with 1 mM EDTA for 5 min at room temperature and replated at 1 x $10^6/cm^2$."*
12.	Zhou et al. 2021	Knee Infrapatellar fat pad cell containing MSCs. Knee arthroscopy therapy.	Less	*"During the knee arthroscopic therapy, partial IPFP tissue was acquired using a standard motorized shaver system. Briefly, 200 mL of the mixture containing fat, synovial tissue, and 0.9% saline was collected by a sterilized arthroscopic setup of the fat collection system connected with suction apparatus. After being filtered twice using a 30-mesh filter (pore size of 550 μm) to remove the synovial tissue, the mixture was centrifuged at 300 × g for 5 min. While the liquid supernatant was discarded, 6 mL of 0.9% saline was used to mix the lipoaspirate to make cell the concentrates. In total, 5mL of the cell concentrates was injected into the corresponding joint cavity, and another 1mL was used for identification by flow cytometry and cultured to determine if the cell concentrates were contaminated ."*

* as defined by CDSCO in Annexure- I of the guideline document

vi. Evidence to Decision Framework:

QUESTION

What is the efficacy and safety of Stem Cell Therapy vs Standard of Care/Usual care in patients with Cartilage Defects?	
POPULATION:	Cartilage Defects
INTERVENTION:	Stem Cell Therapy
COMPARISON:	Standard of Care/ Usual Care
MAIN OUTCOMES:	Reduction in pain and disability, and improvement in function: IKDC Score; KOOS - Activities of Daily Living; KOOS Pain; KOOS QoL; KOOS Sports & Recreation; KOOS Symptom; VAS Score; WOMAC Score; Adverse Events
SETTING:	Hospital/Tertiary Care setting
PERSPECTIVE:	Population
BACKGROUND:	The term 'cartilage defect' refers to a breach in the continuity of the articular cartilage. The etiology of these defects is multifactorial, and can be attributed to trauma, joint instability, or osteoarthritis. Left untreated, these defects can result in significant alteration of joint biomechanics and eventual joint degeneration. The treatment options for focal cartilage defects aim to relieve symptoms, promote cartilage repair, and enhance joint function. The spectrum of management options ranges from conservative management for very small lesions, minimally invasive procedures, cartilage restoration techniques, and joint replacement for large defects with joint destruction.
CONFLICT OF INTERESTST:	None

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○No ○Probably no ○Probably yes ●Yes ○Varies ○Don't know	Cartilage lesions of the knee are common findings in routine arthroscopy. These may lead to pain, swelling, and functional impairment affecting the quality of life. Cartilage injuries limit self-repair potential and often progress to diffuse osteoarthritis that necessitates surgical intervention for symptomatic relief. Several surgical and non-surgical treatments for full-thickness cartilage and osteochondral articular lesions currently exist including microfracture, osteochondral autograft transfer, osteochondral allograft transplantation, and autologous chondrocyte implantation (ACI). However, choosing one treatment over the other remains debatable.[15]	

Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	**VAS:** Evidence from four trials, with a total of 184 participants, reporting the VAS showed a mean difference of -0.81 (95% CI: -1.67 to 0.04) of pain in the stem cell transplantation arm as compared to usual care at the end of 12 months. The difference was statistically non-significant. **WOMAC:** Evidence from three trials, with a total of 172 participants reporting the WOMAC score showed a mean difference of -3.13 (95% CI: -7.87 to 1.60) in the stem cell transplantation arm in comparison to usual care at the end of 12 months. The difference was statistically non-significant. **IKDC:** Evidence from four trials, with a total of 222 participants reporting the IKDC score showed a mean difference of 0.24 (95% CI: -1.27 to 1.76) in the stem cell transplantation arm in comparison to usual care at the end of 12 months, suggesting no statistically significant difference in the two groups. **KOOS Pain:** Evidence from four trials, with a total of 189 participants, reporting the KOOS Pain showed a mean difference of 4.79 (95% CI: 2.28 to 7.31) of pain in the stem cell transplantation arm compared to those on usual care at the end of 12 months. There seems to be a statistically significant decrease in pain, which is less than the MCID of 20 and therefore, unimportant clinically. **KOOS ADL:** Evidence from four trials, with a total of 189 participants, reporting the KOOS ADL showed a mean difference of 2.85 (95% CI: 1.31 to 4.40) in the stem cell transplantation arm compared to those on usual care at the end of 12 months. There seems to be a statistically significant improvement in activities of daily living, which is less than a quarter of the MCID of 20. Therefore, the improvement is unimportant clinically. **KOOS SPR:** Evidence from four trials, with a total of 189 participants, reporting the KOOS SPR showed a mean difference of 4.81 (95% CI: 2.56 to 7.07) in the stem cell transplantation arm compared to those on usual care at the end of 12 months. There seems to be a statistically significant improvement, which is less than a quarter of the MCID of 20. Therefore, the improvement is unimportant clinically. **KOOS Symptom:** Evidence from four trials, with a total of 189 participants, reporting the KOOS Symptom showed a mean difference of 5.14 (95% CI: 2.90 to 7.38) in the stem cell transplantation arm compared to those on usual care at the end of 12 months. There seems to	Considering the MCID of 20% for every outcome, the benefit appears to be trivial

	be a statistically significant improvement, which is a quarter of the MCID of 20. Therefore, the improvement is unimportant clinically. **KOOS QoL:** Evidence from four trials, with a total of 189 participants, reporting the KOOS QoL showed a mean difference of 3.49 (95% CI: -0.04 to 7.02) in the stem cell transplantation arm compared to those on usual care at the end of 12 months. The difference was statistically non-significant.	
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	Only one trial[7] reports serious adverse events and did not report an increase in the incidence of SAE with the use of stem cell therapy as compared to the usual care group. Three serious SAEs occurred in 3 participants in the stem cell group, whereas 2 SAEs occurred in 1 participant in the usual care within the initial 48 weeks. In the 60-month follow-up, 8 SAEs occurred in 7 participants in the stem cell group and 7 SAEs in 5 participants in the usual care group. The events included surgical site pain, pneumonia, femur fracture, myocardial infarction and bone operation.	
Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The evidence in this review is of low to very low quality due to high risk of bias, inconsistency and imprecision in the effect shown by stem cell therapy.	
Values **Is** there important uncertainty about or variability in how much people value the main outcomes?		

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○Important uncertainty or variability ○Possibly important uncertainty or variability ●Probably no important uncertainty or variability ○No important uncertainty or variability	Main outcome is clinical improvement in the form of reduced pain and increased functional activity which is likely to be highly valued by most persons.[16]	
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○Favors the comparison ○Probably favors the comparison ●Does not favor either the intervention or the comparison ○Probably favors the intervention ○Favors the intervention ○Varies ○Don't know	It is less clear if benefits of stem cell intervention outweigh the harms due to trivial benefit, based on limited evidence.	

Resources required How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No direct evidence of the resources required in stem cell transplantation in patients with cartilage defects was identified.	
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ● Moderate ○ High ○ No included studies	No research evidence was identified.	The GDG members were fairly certain that stem cell therapy requires large resources.
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○Favors the comparison ●Probably favors the comparison ○Does not favor either the intervention or the comparison ○Probably favors the intervention ○Favors the intervention ○Varies ○No included studies	No research evidence was identified.	The intervention was not found to be effective and hence the committee deferred to comment on cost effectiveness.
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○Reduced ●Probably reduced ○Probably no impact ○Probably increased ○Increased ○Varies ○Don't know	No research evidence was identified. As stem cell therapy is an expensive treatment offered only at tertiary care centers, it is likely to increase inequity as it would not be affordable by all.	As stem cell therapy is an expensive treatment offered only at tertiary care centers, it is likely to increase inequity as it would not be affordable by all.
Acceptability		

Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○No ○Probably no ●Probably yes ○Yes ○Varies ○Don't know	Despite uncertainty regarding the medical risks and benefits associated with stem cell injections, patients with cartilage defects have very high expectations from stem cell therapy.[17]	
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○No ○Probably no ●Probably yes ○Yes ○Varies ○Don't know	No research evidence was identified. Stem Cell transplantation can be performed only in tertiary care centers so feasibility in lesser equipped hospitals and clinics is not possible.	Feasible to implement in tertiary centers.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know

	JUDGEMENT						
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	**Moderate**	High			No included studies
COST EFFECTIVENESS	Favors the comparison	**Probably favors the compariso n**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Use only in the context of rigorously conducted RCTs	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	●	○	○	○

CONCLUSIONS

Recommendation

Stem Cell Therapy is **not recommended** in routine practice for the treatment of cartilage defects. It is recommended only in the context of rigorously conducted randomized controlled trials.

Justification

This recommendation has been made as there is very low certainty evidence of trivial reduction in pain and no improvement in function. There is little or no difference in undesirable effects between stem cell therapy and usual care. In addition, the follow up period is limited to comment on the long-term safety of stem cell therapy. Results should be interpreted with caution, in view of various study limitations such as small number of participants and/or events, risk of bias and different sources of stem cell used.

vii. Data extraction:

Data extraction methods:

Data was extracted using pre-piloted data extraction and tagging features available on the Nested Knowledge platform. Two independent reviewers performed the data extraction. Extracted data included several baseline data items, details of interventions and controls and outcome measures. A third reviewer checked the extracted data for accuracy.

Risk of bias assessment: Risk of bias was assessed by the Cochrane Risk of Bias 2 (RoB 2) tool performed by two independent reviewers. A third reviewer adjudicated in the cases of any conflict.

Synthesis Methods & Assessment of Heterogeneity: Both qualitative and quantitative data analysis was performed. For qualitative analysis, appropriate tables and figures were constructed to summarize the key baseline and outcome variables. Quantitative synthesis was performed by comparing stem cell therapies to control interventions. The RevMan Web software package was used for performing

head-to-head meta-analyses. Continuous data were summarized using MD, and RR was determined for categorical outcomes. Confidence intervals (95%) were determined for each meta-analysis estimated followed by construction of forest plots to visualize the results. Heterogeneity was explored both clinically and statistically. Statistical heterogeneity was explored by means of the I^2 statistic and determining the Chi-squared test P Value. A fixed-effects model meta-analysis was used if the heterogeneity, as assessed by the I^2 statistic was <50%. If the I^2 statistic was >50% then the PICO of each study is reviewed. If the heterogeneity could be explained by the differences in the PICO, then subgroup analyses was conducted. If no critical differences were observed in the PICO, then the random-effects model was used to pool the results of all the included studies.

Data Extraction Sheet:

Study	Wong et al. 2013[1]
Study type:	RCT
Number of participants:	56
Countries and setting:	Singapore
Duration of study Follow up (post intervention):	6, 12 & 24 months
Method of assessment of disease condition:	MRI
Subgroup analysis within study	
Inclusion criteria:	Medial compartment OA with genu varum in patients younger than 55 years, diagnosed arthroscopically/radiologically, normal lateral joint space, no fixed flexion deformity of knee and no collateral ligament instability.
Exclusion criteria:	• Joint line congruity angle more than 2. • Malalignment of knee from femoral causes and bi-compartmental and tri-compartmental osteoarthritis. • Patient who cannot tolerate MRI scans, unable to answer subjective questions or not mentally fit to provide informed consent.
Recruitment/selection of patients:	RCT
Intervention: Type of stem cells with method of their characterization, Route of administration, Dose	Bone Marrow derived stem cell therapy. High Tibial Osteotomy (HTO)

Outcomes reported with time points	• IKDC • Tegner • Lysholm • MOCART
Funding	
RoB2 Assessment: Specify separately for each domain	D1: Some concern D2: Low D3: Low D4: High D5: Some concern. Overall: High
Study	Akgun et al. 2015[2]
Study type:	RCT
Number of participants:	14
Countries and setting:	Turkey
Duration of study Follow up (post intervention):	6, 12 & 24 months
Method of assessment of disease condition:	MRI
Subgroup analysis within study	
Recruitment/selection of patients:	RCT
Inclusion criteria:	• Patient is able to provide informed consent. • Patient is over the age of 18 years. • Patient who are willing and able to attend all follow up visits. • Patient with a symptomatic traumatic isolated single full thickness femoral condylar defects in the knee. **In the opinion of the investigator the patient is a candidate for cartilage repair surgery:** • Patient is in stable health. • Stable Knee and in anatomical alignment. • More than 50% of the normal meniscal volume. **The following previous procedures are acceptable:** • Meniscectomy (resection of less than 50 % of the medial or lateral meniscus). • Meniscal repair.

	• Patients who have had previous ACL reconstruction are eligible only if they have been able to complete 6 months of rehabilitation. • Female patients are not pregnant at time of surgery and do not plan on becoming pregnant during the course of the study BMI of30 kg/m^2.
Exclusion criteria:	• Alcohol or drug abuse • Patient has had intra-articular steroid injection into the study knee within the previous 3 months • Ipsilateral hip disease as determined by pain or restricted range of motion onphysical examination • Severe vascular or neurological disease, uncontrolled diabetes, or history of autoimmune disease • Evidence of degenerative arthritis on radiographs • Presence of active infection at the defect site • Patients taking medications or under treatments(s) known to have an effect onbone metabolism such as, but not limited to bisphosphonates, • chemotherapeutic or immunosuppressive agents • Patients taking medications or under treatment(s) known to have an effect onbone metabolism such as, but not limited to bisphosphonates, • chemotherapeutic or immunosuppressive agents
Intervention: Type of stem cells with method of their characterization, Route of administration, Dose	• Synovium derived stem cell therapy. • Autologous chondrocyte implantation (ACI).
Outcomes reported with time points	• VAS • KOOS • Tegner
Funding	
RoB2 Assessment: Specify separately for each domain	D1:Low D2:Low D3:Low D4:Low D5:Some concern. Overall: Some concern
Study	Koh et al. 2016[3]
Study type:	RCT

Number of participants:	80
Countries and setting:	Korea
Duration of study Follow up (post intervention):	3 & 12 months
Method of assessment of disease condition:	MRI
Subgroup analysis within study	
Inclusion criteria:	• Patients considered eligible for inclusion were men and women (aged 18 to 50 years) who had a single International Cartilage Repair Society ICRS) grade III/IV symptomatic cartilage lesion (≥3 cm^2) on the femoral condyle diagnosed on preoperative magnetic resonance imaging (MRI) in a stable and well-aligned knee with minimal additional injury.
Exclusion criteria:	• Any knee joint operation within 6 months before the screening. • ICRS grade III/IV defects on the patella or tibia. • Symptomatic musculoskeletal conditions in the lower limbs that could affect the evaluation of the target knee. • Previous total meniscectomy, meniscal allograft, or bucket-handle tears or displaced tears that required removal of more than 50% of the meniscus in the target knee. • Malalignment that required osteotomy to correct tibiofemoral or patellofemoral alignment. • K-L grade 3 or 4 osteoarthritis. • Inflammatory disease or other conditions that affected the joints and septic arthritis within 1 year before the screening.
Recruitment/selection of patients:	RCT
Intervention: Type of stem cells with method of their characterization, Route of administration, Dose	Adipose Derived MSC.
Outcomes reported with time points	VAS KOOS Lysholm
Funding	

RoB2 Assessment: Specify separately for each domain	D1:Some concern D2:Low D3:Some concern D4:Low D5:Some concern Overall: Some concern
Study	Hong et al. 2019[4]
Study type:	RCT
Number of participants:	32
Countries and setting:	China
Duration of study Follow up (post intervention):	6 & 12 months
Method of assessment of disease condition:	MRI
Subgroup analysis within study	
Inclusion criteria:	• Age 18–70 years old. • Bilateral knees with Grade II-III osteoarthritis, identified by two different observers, according to the K-L grading scale. • Bilateral knees with initial pain evaluated at four or greater on a ten-point visual analog scale (VAS). • Patient is able to understand the instructions given by the doctors. • Signing informed consent form.
Exclusion criteria:	• Arthritis, post-infectious arthritis, and previous articular fractures). • Had secondary arthritis (related to rheumatoid arthritis, gouty). • Severe heart, lung, liver, and kidney disease that cannot tolerate. • General anesthesia. • Psychiatric disorders. • History of liposarcoma and other cancer. • Pregnancy. • Immunosuppression. • Coagulopathy. • Abdominal hernia. • Any knee joint operation or intra-articular injection of any drug within 6 months before

	the screening. • Sign of infection or serological positive of HIV, syphilis. • A low level of body fat content that may make liposuction difficult.
Recruitment/selection of patients:	RCT
Intervention: Type of stem cells with method of their characterization, Route of administration, Dose	• Adipose Derived SVF. • Intra-articular injection of hyaluronic acid.
Outcomes reported with time points	• VAS • WOMAC • MOCART • WORMS
Funding	
RoB2 Assessment: Specify separately for each domain	D1:Low D2:Low D3:Low D4:Low D5:Low Overall: Low
Study	Lee et al. 2019[5]
Study type:	RCT
Number of participants:	24
Countries and setting:	Korea
Duration of study Follow up (post intervention):	3 & 6 months
Method of assessment of disease condition:	MRI
Subgroup analysis within study	
Inclusion criteria:	• Eligible patients were between 18 and 75 years of age with osteoarthritis of the knee joint and had a mean pain intensity of 4 or more on a 10-point visual analog scale (VAS) for at least 12 weeks. • Patients underwent physical examination; laboratory tests such as routine blood and urine tests, serologic test, tumor screening, electrocardiogram, and pregnancy test if indicated; and MRI of the knee at screening with informed consent. • To objectively assess cartilage regeneration, the patients with at least one focal or

	localized grade 3 or 4 lesion on MRI scan. • All pain medications were discontinued except the rescue analgesic.
Exclusion criteria:	
Recruitment/selection of patients:	RCT
Intervention: Type of stem cells with method of their characterization, Route of administration, Dose	• Adipose Derived MSC
Outcomes reported with time points	• VAS • KOOS • WOMAC
Funding	
RoB2 Assessment: Specify separately for each domain	D1:High D2:Low D3:Low D4:Low D5:Some concern Overall: High
Study	Hashimoto et al. 2019[6]
Study type:	RCT
Number of participants:	11
Countries and setting:	Japan
Duration of study Follow up (post intervention):	12 months
Method of assessment of disease condition:	MRI
Subgroup analysis within study	
Inclusion criteria:	• Indication for bone marrow stimulation. • ICRS articular cartilage injury classification SGrade 3 Size of defect S 2cm^2 Kellgren Lawrence OA grade S3 Age between 16 and 70 years.
Exclusion criteria:	• Operative history of ACL and/or PCL reconstruction the last 2 months International Cartilage Repair Society (ICRS) articular cartilage injury classification Malignancy. • K-L OA grade S3. • Pregnant woman.

	• Infectious diseases (HBV, HCV, ATLA, HIV) Mental disorders. • Contraindications to a general anesthesia Unable to adhere to trial.
Recruitment/selection of patients:	RCT
Intervention: Type of stem cells with method of their characterization, Route of administration, Dose	• Bone Marrow Derived MSC.
Outcomes reported with time points	IKDC KOOS MOCART
Funding	
RoB2 Assessment: Specify separately for each domain	D1:Some concern D2:High D3:Low D4:High D5:Some concern Overall: High
Study	Lim et al. 2021[7]
Study type:	RCT
Number of participants:	89
Countries and setting:	Korea
Duration of study Follow up (post intervention):	3 & 6MRI months
Method of assessment of disease condition:	
Subgroup analysis within study	
Inclusion criteria:	• Male or female patients aged 18 years or older. • Lesion size of 2-9 cm^2 in 1 compartment (the compartment with the most prominent symptoms). • Joint swelling, tenderness, and limitation of active range of motion of grade 2. • Pain 60 mm on a 100-mm visual analog scale in the affected joint. • Adequate blood coagulation activity: prothrombin time (international normalized ratio)2.0 mg/dL; proteinuria measured with dipstick of trace or less. • Adequate hepatic function: bilirubin 2.0 mg/dL; aspartate aminotransferase/alanine aminotransferase 100 IU/L.

	• No surgery or radiation therapy in the affected joint within the past 6 weeks, and recovery from past treatments. • For women of childbearing potential, agreement to practice adequate birth control during the study. • Agreement to participate and signed informed consent.
Exclusion criteria:	• Current or past history of autoimmune disease. • Infectious disease requiring antibiotics. • Current or past myocardial infarction, ischemic heart failure, other serious heart conditions, or uncontrolled hypertension. • Serious medical comorbidity. • Current pregnancy or nursing Current or past psychotic diseases or epilepsy. • Alcohol abuse. • Heavy smoking. • Chronic inflammatory articular disease such as rheumatoid arthritis. • Current enrollment in any other clinical trial. • Immunosuppressant use within the past 6 week. • Ligament instability of grade 2a on physical examination. • Known history of hypersensitivity or allergy to gentamicin. • Any other condition for which the principal investigator considers the patient inappropriate for participation in the trial (such as K-L grade 4 osteoarthritis, significant deformity, or previous osteotomy).
Recruitment/selection of patients:	RCT
Intervention: Type of stem cells with method of their characterization, Route of administration, Dose	• Umblical Cord Blood Derived MSC. • Microfracture.
Outcomes reported with time points	• VAS • IKDC • WOMAC • ICRS Grade of Improvement • ICRS Histological Score
Funding	

RoB2 Assessment: Specify separately for each domain	D1:Some concern D2:Some concern D3:Some concern D4:Low D5:Some concern Overall: Some concern
Study	Saw et al. 2021[8]
Study type:	RCT
Number of participants:	69
Countries and setting:	USA and Malaysia
Duration of study Follow up (post intervention):	6, 12, 18 and 24 months
Method of assessment of disease condition:	
Subgroup analysis within study	
Inclusion criteria:	• Patients aged 18 to 55 years with International Cartilage Repair Society grade 3 and 4 chondral lesions. • Patients with single or multiple lesions were included with at least 1 of the lesions ≥3 cm 2. • Bipolar, patellofemoral, femorotibial lesions and previously failed cartilage repair procedures were allowed and not exclusionary factors.
Exclusion criteria:	• Exclusion criteria were 3 previous surgical interventions, varus or valgus deformity more than 40% into the medial or lateral compartment, preoperation flexion deformity more than 10°, ligament deficiency, and body mass index ≥35 kg/m^2.
Recruitment/selection of patients:	RCT
Intervention: Type of stem cells with method of their characterization, Route of administration, Dose	PBSC Plus HA
Outcomes reported with time points	• IKDC • KOOS • NRS
Funding	

RoB2 Assessment: Specify separately for each domain	D1:Some concern D2:Low D3:Low D4:High D5:Low Overall: High
Study	Liu et al. 2021[9]
Study type:	RCT
Number of participants:	15
Countries and setting:	Taiwan
Duration of study Follow up (post intervention):	12 and 24 months
Method of assessment of disease condition:	MRI
Subgroup analysis within study	
Inclusion criteria:	
Exclusion criteria:	
Recruitment/selection of patients:	RCT
Intervention: Type of stem cells with method of their characterization, Route of administration, Dose	Kartigen Microfracture
Outcomes reported with time points	VAS IKDC
Funding	
RoB2 Assessment: Specify separately for each domain	D1:Some concern D2:Some concern D3:Low D4:Some concern D5:Low Overall: Some concern
Study	Kim et al. 2022[10]
Study type:	RCT
Number of participants:	26

Countries and setting:	Korea
Duration of study Follow up (post intervention):	3, 6 & 12 months
Method of assessment of disease condition:	MRI
Subgroup analysis within study	
Inclusion criteria:	• Age between 20 and 80 years old. • BMI <30 Kg/m. • K-L grade 2 to 4. • Diagnosis of primary osteoarthritis of knee. • Patient is able to understand the instruction by doctor and to complete the questions required for the study.
Exclusion criteria:	• Patient with measure twice or more than normal in lab test or with any condition that principal investigator considers clinically important. • Patient with serious conditions such as cardiovascular diseases, renal disease, liver diseases, cancer or diabetes. • Osteoporosis. • Females who are pregnant, lactating or planning pregnancy. • Patient positive for screening test of human immunodeficiency, hepatitis B or C. • Patient who received contraindicated drugs without wash out period for this study. • Patients who had participated in other clinical trails within 12 weeks before the screening.
Recruitment/selection of patients:	RCT
Intervention: Type of stem cells with method of their characterization, Route of administration, Dose	• Adipose Derived MSC • HTO alone
Outcomes reported with time points	• KOOS • WOMAC • ICRS • MOCART
Funding	

RoB2 Assessment: Specify separately for each domain	D1:Some concern D2:Some concern D3:Low D4:Low D5:Low Overall: Some concern
Study	Venosa et al. 2022[11]
Study type:	RCT
Number of participants:	38
Countries and setting:	Italy
Duration of study Follow up (post intervention):	3, 6 & 12 months
Method of assessment of disease condition:	MRI
Subgroup analysis within study	
Inclusion criteria:	• Age between 20 and 80 years old. • BMI <30 Kg/m. • K-L grade 2 to 4. • Diagnosis of primary osteoarthritis of knee. • Patient is able to understand the instruction by doctor and to complete the questions required for the study.
Exclusion criteria:	• Patient with measure twice or more than normal in lab test or with any condition that principal investigator considers clinically important. • Patient with serious conditions such as cardiovascular diseases, renal disease, liver diseases, cancer or diabetes. • Osteoporosis. • Females who are pregnant, lactating or planning pregnancy. • Patient positive for screening test of human immunodeficiency, hepatitis B or C. • Patient who received contraindicated drugs without wash out period for this study. • Patients who had participated in other clinical trails within 12 weeks before the screening.
Recruitment/selection of patients:	RCT

Intervention: Type of stem cells with method of their characterization, Route of administration, Dose	• Adipose Derived MSC • HTO alone
Outcomes reported with time points	• KOOS • WOMAC • ICRS • MOCART
Funding	
RoB2 Assessment: Specify separately for each domain	D1:Some concern D2:Some concern D3:Low D4:Low D5:Low Overall: Some concern
Study	De Girolamo et al. 2019[12]
Study type:	RCT
Number of participants:	24
Countries and setting:	Italy
Duration of study Follow up (post intervention):	6, 12 & 24 months
Method of assessment of disease condition:	MRI
Subgroup analysis within study	
Inclusion criteria:	• Age between 18 and 55 years. • One or two grade III or IV articular surface lesions of the knee according to the International Cartilage Repair Society's chondral defect classification system (ICRS), lesion size between 2 and 8 cm^2, and normal surrounding cartilage (accepted one or two grade I/II chondral lesions).
Exclusion criteria:	• Patients with more than two chondral defects, immuno-mediated pathologies including osteoarthritis, knee infection, untreatable instability, malalignment or meniscal tears, serious cardiologic pathologies, or problematic general conditions were excluded from the study.
Recruitment/selection of patients:	RCT

Intervention: Type of stem cells with method of their characterization, Route of administration, Dose	• BMAC • AMIC
Outcomes reported with time points	• KOOS • Lysholm
Funding	
RoB2 Assessment: Specify separately for each domain	D1:Some concern D2:Some concern D3:Low D4:Low D5:Low Overall: Some concern
Study	Saw et al. 2013[13]
Study type:	RCT
Number of participants:	49
Countries and setting:	United Kingdom
Duration of study Follow up (post intervention):	6, 12, 18 and 24 months
Method of assessment of disease condition:	MRI
Subgroup analysis within study	
Inclusion criteria:	• Male and female patient between the age of 18 and 50 years, with ICRS grade 3 and 4 lesion of knee joint.
Exclusion criteria:	• History of more than one surgery of knee in question or previous lower extremity amputation or significant peripheral vascular disease. • BMI of 35 or geator. • Varus deformity of more than 10 degree. • A positive pregnancy test. • Deformity requiring osteotomy or complex surgery.
Recruitment/selection of patients:	RCT
Intervention: Type of stem cells with method of their characterization, Route of administration, Dose	• PBSC + HA

Outcomes reported with time points	• IKDC • ICRS II
Funding	
RoB2 Assessment: Specify separately for each domain	D1:High D2:Low D3:Low D4:Low D5:Low Overall: Some concern
Study	Zhou et al. 2021[14]
Study type:	RCT
Number of participants:	57
Countries and setting:	China
Duration of study Follow up (post intervention):	3, 6 & 12 months
Method of assessment of disease condition:	MRI
Subgroup analysis within study	
Inclusion criteria:	• Patients between the ages of 18 and 75 years. MRI clearly indicated articular cartilage injury, and the Kellgren-Lawrence standard knee grade was not more than level-3. • Patients with obvious knee pain or discomfort lasting for more than 3 months. • Patients who were willing to participate in the study and signed the informed consent form. • Patients who had articular cartilage injury diagnosed by arthroscopy and who did not receive targeted treatment.

Exclusion criteria:	• Other surgical procedures were performed to treat the articular cartilage. • Patients who had a history of intra-articular injection or peri-articular invasive treatments and procedures within 3 months. • Symptoms and imaging findings that were localized in the patellofemoral joint. • Patients who suffered from malignant neoplasms. • Patients who had active infection in other parts of the body. • Female patients who were pregnant, Page 5/17 lactating, or preparing for pregnancy. • Cartilage lesions caused by infectious or gouty arthritis. • Patients who had autoimmune diseases such as rheumatoid arthritis and ankylosing spondylitis. • Patients who had diabetes with FBG over 8 mmol/L and had poor control. • Patients who were generally in poor condition and unable to tolerate surgery. • Patients who had severe diseases such as cerebral hemorrhage, severe pneumonia, and multiple organ dysfunction. • Patients with Charcot joint. • Any conditions that might increase the patient's risk or influence the results of the experiment during the research. • Other reasons making the patient unsuitable for this study.
Recruitment/selection of patients:	RCT
Intervention: Type of stem cells with method of their characterization, Route of administration, Dose	• Knee Infrapatellar fat pad cell containing MSCs. • Knee arthroscopy therapy.
Outcomes reported with time points	• VAS • WOMAC • MOCART
Funding	
RoB2 Assessment: Specify separately for each domain	D1:Low D2:Low D3:Low D4:Low D5:Low Overall: Low

viii. List of excluded studies:

Title	Author	Publication Year	Final Screening Status
Present status and perspective of articular cartilage regeneration.	Wakitani, Shigeyuki	2007	Excluded: Non-randomized clinical trial
Repair of articular cartilage defects in the patello-femoral joint with autologous bone marrow mesenchymal cell transplantation: three case reports involving nine defects in five knees.	Wakitani, Shigeyuki	2007	Excluded: Case Report
Safety of autologous bone marrow-derived mesenchymal stem cell transplantation for cartilage repair in 41 patients with 45 joints followed for up to 11 years and 5 months.	Wakitani, Shigeyuki	2011	Excluded: Non-randomized clinical trial
Freshly isolated stromal cells from the infrapatellar fat pad are suitable for a one-step surgical procedure to regenerate cartilage tissue.	Jurgens, Wouter J F M	2009	Excluded: Non-randomized clinical trial
Isolation and cultivation of mesenchymal stem cells from iliac crest bone marrow for further cartilage defect management.	Lubis, Andri M T	2011	Excluded: Non-randomized clinical trial
Treatment of chondral defects of the knee with one step matrix-assisted technique enhanced by autologous concentrated bone marrow: in vitro characterisation of mesenchymal stem cells from iliac crest and subchondral bone.	de Girolamo, Laura	2010	Excluded: Non-randomized clinical trial
Cell-based therapy improves function in adolescents and young adults with patellar osteochondritis dissecans.	Teo, Bryon J X	2013	Excluded: Non-randomized clinical trial
Matrix-associated stem cell transplantation (MAST) in chondral defects of foot and ankle is effective.	Richter, Martinus	2013	Excluded: Non-randomized clinical trial
Clinical outcomes of mesenchymal stem cell injection with arthroscopic treatment in older patients with osteochondral lesions of the talus.	Kim, Yong Sang	2013	Excluded: Non-randomized clinical trial
A novel, minimally-invasive technique of cartilage repair in the human knee using arthroscopic microfracture and injections of mesenchymal stem cells and hyaluronic acid--a prospective comparative study on safety and short-term efficacy.	Lee, Kevin B L	2012	Excluded: Non-randomized clinical trial
Osteochondral lesions of the knee reconstructed with mesenchymal stem cells - results.	SkowroÅ„ski, Jan	2013	Excluded: Non-randomized clinical trial

Comparative outcomes of open-wedge high tibial osteotomy with platelet-rich plasma alone or in combination with mesenchymal stem cell treatment: a prospective study.	Koh, Yong-Gon	2014	Excluded: Non-randomized clinical trial
Does an injection of a stromal vascular fraction containing adipose-derived mesenchymal stem cells influence the outcomes of marrow stimulation in osteochondral lesions of the talus? A clinical and magnetic resonance imaging study.	Kim, Yong Sang	2014	Excluded: Non-randomized clinical trial
In Situ Recruitment of Human Bone Marrow-Derived Mesenchymal Stem Cells Using Chemokines for Articular Cartilage Regeneration.	Park, Min Sung	2015	Excluded: Experimental study
Matrix-Induced Autologous Chondrocyte Implantation versus Multipotent Stem Cells for the Treatment of Large Patellofemoral Chondral Lesions: A Nonrandomized Prospective Trial.	Gobbi, Alberto	2015	Excluded: Non-randomized clinical trial
Arthroscopic Transplantation of Synovial Stem Cells Improves Clinical Outcomes in Knees with Cartilage Defects.	Sekiya, Ichiro	2015	Excluded: Non-randomized clinical trial
One-step surgery with multipotent stem cells and Hyaluronan-based scaffold for the treatment of full-thickness chondral defects of the knee in patients older than 45Âyears.	Gobbi, Alberto	2017	Excluded: Non-randomized clinical trial
Adipose derived mesenchymal stem cell therapy in the treatment of isolated knee chondral lesions: design of a randomised controlled pilot study comparing arthroscopic microfracture versus arthroscopic microfracture combined with postoperative mesenchymal stem cell injections.	Freitag, Julien	2015	Excluded: Study Protocol
Bone Marrow Concentrate Improves Early Cartilage Phase Maturation of a Scaffold Plug in the Knee: A Comparative Magnetic Resonance Imaging Analysis to Platelet-Rich Plasma and Control.	Krych, Aaron J	2016	Excluded: Non-randomized clinical trial
Arthroscopic Bone Marrow Stimulation and Concentrated Bone Marrow Aspirate for Osteochondral Lesions of the Talus: A Case-Control Study of Functional and Magnetic Resonance Observation of Cartilage Repair Tissue Outcomes.	Hannon, Charles P	2016	Excluded: Non-randomized clinical trial
Focal cartilage defects in the knee - a randomized controlled trial comparing autologous chondrocyte implantation with arthroscopic debridement.	Randsborg, Per-Henrik	2016	Excluded: Study Protocol
Equivalent 10-Year Outcomes After Implantation of Autologous Bone Marrow-Derived Mesenchymal Stem	Teo, Alex QuokAn	2019	Excluded: Non-randomized

Cells Versus Autologous Chondrocyte Implantation for Chondral Defects of the Knee.			clinical trial
A novel autologous-made matrix using hyaline cartilage chips and platelet-rich growth factors for the treatment of full-thickness cartilage or osteochondral defects: Preliminary results.	Cugat, RamÃ³n	2020	Excluded: Non-randomized clinical trial
Comparison of Bone Marrow Aspirate Concentrate and Allogenic Human Umbilical Cord Blood Derived Mesenchymal Stem Cell Implantation on Chondral Defect of Knee: Assessment of Clinical and Magnetic Resonance Imaging Outcomes at 2-Year Follow-Up.	Ryu, Dong Jin	2020	Excluded: Non-randomized clinical trial
Autologous chondrocytes versus filtered bone marrow mesenchymal stem/stromal cells for knee cartilage repair-a prospective study.	Martin A, David	2021	Excluded: Non-randomized clinical trial
Comparison of Clinical and Radiographic Outcomes Following Arthroscopic Debridement With Extracellular Matrix Augmentation and Osteochondral Autograft Transplantation for Medium-Size Osteochondral Lesions of the Talus.	Hansen, Oliver B	2021	Excluded: Non-randomized clinical trial
Clinical Efficacy and Safety of the Intra-articular Injection of Autologous Adipose-Derived Mesenchymal Stem Cells for Knee Osteoarthritis: A Phase III, Randomized, Double-Blind, Placebo-Controlled Trial.	Kim, Kang-Il	2023	Excluded: Not related to cartilage defect
Tissue Engineering, Embryonic, Organ and Other Tissue Specific Stem Cells: Scaffold-free pellet-type autologous chondrocyte implantation (CARTILIFEÂ®) for for the restoration of articular cartilage defects: a randomized phase 2 clinical trial and extended 5-year clinical follow-up	Lee, E.	2022	Excluded: Conference Abstract
The Effect of Cell Dose on the Early Magnetic Resonance Morphological Outcomes of Autologous Cell Implantation for Articular Cartilage Defects in the Knee: A Randomized Clinical Trial	Niemeyer, P	2016	Excluded: Did not evaluate stem cell therapy
Functional Medium-Term Results After Autologous Matrix-Induced Chondrogenesis for Osteochondral Lesions of the Talus: A 5-Year Prospective Cohort Study	Gottschalk, O	2017	Excluded: Non-randomized clinical trial
Efficacy and safety of adult human bone marrow-derived, cultured, pooled, allogeneic mesenchymal stromal cells (StempeucelÂ®): preclinical and clinical trial in osteoarthritis of the knee joint	Gupta, PK	2016	Excluded: Not related to cartilage defect
Infrapatellar fat pad-derived mesenchymal stem cell therapy for knee osteoarthritis	Koh, YG	2012	Excluded: Non-randomized clinical trial

Intra-articular injection of two different doses of autologous bone marrow mesenchymal stem cells versus hyaluronic acid in the treatment of knee osteoarthritis: multicenter randomized controlled clinical trial (phase I/II)	Lamo-Espinosa, JM	2016	Excluded: Not related to cartilage defect
Treatment of Knee Osteoarthritis with Allogeneic Bone Marrow Mesenchymal Stem Cells: A Randomized Controlled Trial	Vega, A	2015	Excluded: Not related to cartilage defect
Adipose Mesenchymal Stromal Cell-Based Therapy for Severe Osteoarthritis of the Knee: A Phase I Dose-Escalation Trial.	Pers, Yves-Marie	2016	Excluded: Not related to cartilage defect
Human adipose-derived mesenchymal stem cells for osteoarthritis: a pilot study with long-term follow-up and repeated injections.	Song, Yang	2018	Excluded: Not related to cartilage defect
Treatment of knee osteoarthritis with intra-articular injection of autologous adipose-derived mesenchymal progenitor cells: a prospective, randomized, double-blind, active-controlled, phase IIb clinical trial.	Lu, Liangjing	2019	Excluded: Not related to cartilage defect
Multi-compositional MRI evaluation of repair cartilage in knee osteoarthritis with treatment of allogeneic human adipose-derived mesenchymal progenitor cells.	Zhao, Xinxin	2019	Excluded: Non-randomized clinical trial

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4. TENDINOPATHY

i. **Key question in PICO format**

ii. **Search strategy**

iii. **PRISMA flow diagram**

iv. **Summary of included studies**

v. **Classification of studies based on level of stem cell manipulation**

vi. **Evidence to decision framework**

vii. **Data extraction**

viii. **List of excluded studies**

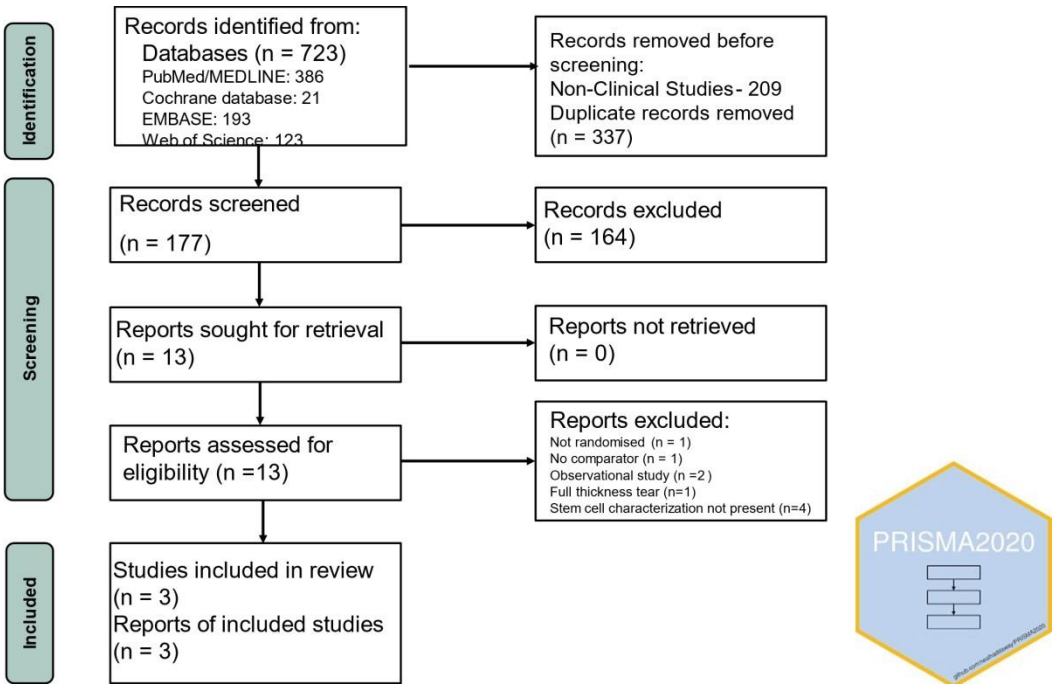
i. Key question in PICO format:

Population: Patients with Tendinopathy
Intervention: Any Stem cell and product derived from stem cells
Comparator: Usual Care/ Conventional Care
Critical Outcomes: Efficacy: Reduction in pain, Disability; Safety: Severe Adverse Events

ii. Search strategy (September 2023):

A literature search was conducted on PubMed/MEDLINE, EMBASE, Web of Science, and Cochrane CENTRAL. The search terms were formed using medical subject headings along with Boolean operators. The search terms for the PubMed were (Tendinopathy[MeSH] OR Tendinopathy OR Tendon OR "Tendon disorder" OR "Tendon injuries" OR Tendinosis OR Tendinitis OR "Tennis elbow"[MeSH] OR "Elbow Tendinopathy"[MeSH] OR "Tennis elbow" OR "Lateral epicondylitis" OR "Lateral epicondylosis" OR "Golfer s elbow" OR "Rotator Cuff"[MeSH] OR "Rotator cuff" OR "Rotator Cuff Injuries"[MeSH] OR "De Quervain Disease"[MeSH] OR "De Quervain disease" OR "Jumper s knee" OR "Patellar tendon" OR Achilles OR "Achilles Tendon"[MeSH]) AND ("Stem Cells"[MeSH] OR "Stem cells" OR "Mesenchymal Stem Cells"[MeSH] OR "Mesenchymal stem cells" OR "Progenitor cells" OR "Mother cells" OR Multipotent OR Pluripotent OR Totipotent) AND Humans[Filter]. Search terms were adapted for other databases.

iii. PRISMA flow diagram:



iv. Summary of included studies:

Study	Population	Intervention	Comparison	Outcomes	Comments
Chun et al. 2022 Republic of Korea[1]	Patients >18 years of age with persistent shoulder pain lasting more than 3 months despite conservative management	Allogenic adipose tissue derived mesenchymal stem cells with fibrin glue	Active control: Fibrin glue + normal saline Control: Normal saline	• VAS • ASES • MRI: tear size improved/No change) • Adverse events	Stem cell injection was not more effective than control injections
Rodas et al. 2021 Spain[2]	Patients 18-48 years of age with unilateral patellar tendinopathy with intratendinous lesion > 3 mm	Bone marrow mesenchyme stem cells	Leukocyte poor Platelet rich plasma	• VAS • VISA-P • UTC • USG • MRI • Adverse events	Patients receiving MSCs showed a greater improvement than Lp-PRP
Rosario et al. 2021 Brazil[3]	Patients, 18-73 years of age, with clinical and radiological diagnosis of gluteal tendinopathy	Bone marrow aspirate concentrate	Corticosteroid	• VAS • EmoQoL Lequesne	BMAC is a safe technique with promising results

v. Classification of studies on the basis of level of manipulation of the stem cell/ Stem cell derived product used (*interpreted by the Secretariat as defined by CDSCO* and the information provided in the trial itself*):

S. No.	Trial Details	Intervention	Level of manipulation	Information extracted from trial
1.	Chun et al. 2022	Allogenic adipose tissue derived mesenchymal stem cells with fibrin glue	More	*"The intervention group received commercial allogenic adipose tissue-derived adult MSC (Anterogen, Seoul) with fibrin glue10 as scaffold."*

2.	Rodas et al. 2021	Autologous expanded bone marrow mesenchymal stem cells (BM-MSCs)	More	*"Cells were processed using GMP conditions in the Cell Production Center. The mononuclear fraction was isolated by gradient centrifugation (Ficoll-Plaque; GE Healthcare Bio-Sciences, AB), resuspended, and cultured in MSC expansion culture medium."*
3.	Rosario et al. 2021	Bone marrow aspirate concentrate	Less	*"Cell counting and viability assessment were performed using a small cells suspension at the procedure site. Live cells were sampled by anti-CD34 antibody staining and Propidium Iodide incorporation."*

* as defined by CDSCO in Annexure- I of the guideline document

vi. Evidence to decision framework:

QUESTION

Should Stem cell vs. standard of care be used for Tendinopathy?	
POPULATION:	Tendinopathy
INTERVENTION:	Stem cell
COMPARISON:	standard of care
MAIN OUTCOMES:	Pain, Functional Score, Serious Adverse Events
SETTING:	Hospital/ Tertiary Care setting
PERSPECTIVE:	Population
BACKGROUND:	Tendinopathy is a common disorder in athletes and the general population and is characterized by pain and swelling in addition to functional limitations. Several pharmacological (Corticosteroids, non-steroidal anti-inflammatory drugs, etc.) and surgical therapies have been used over time. Though symptomatic relief has been achieved with these management strategies, recalcitrant cases are present in plenty. Thus, there remains an unmet need to search for new options for treatment of tendinopathy.
CONFLICT OF INTERESTS:	None

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○No ○Probably no ○Probably yes ●Yes ○Varies ○Don't know	Tendinopathy or tendinosis is a common condition seen in individuals of all age groups, most frequently in the active adult population commonly caused due to sports related injuries. The disorder is characterized by localized tenderness and pain, which is significantly exacerbated when the load on the tendon is increased, resulting in loss of function and performance.[4,5]	
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
●Trivial ○Small ○Moderate ○Large ○Varies ○ Don't know	**VAS 0-10:** Evidence from three trials, with a total of 75 participants, reporting the VAS showed a mean difference of mean difference of -1.56 (95% CI: -2.42 to -0.69) in the stem cell transplantation arm as compared to those on usual care at the end of 6 months. There seems to be a statistically significant decrease in pain, which does not cross the MCID of 2. Therefore, the reduction in pain is unimportant clinically. **ASES 0-100:** Evidence from one trial, with a total of 15 participants reporting the ASES score showed a mean difference of -0.30 (95% CI: -24.23 to 23.63) in the stem cell transplantation arm in comparison to usual care at the end of 3 months. The difference was statistically non-significant.	Considering the MCID of 20%, the benefit appears to be trivial.

Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	None of the trials reported serious adverse events. The evidence is insufficient to draw firm conclusions due to limited long term follow up of trials.	
Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The evidence in this review is of low to very low quality due to high risk of bias, inconsistency and imprecision in the effect shown by stem cell therapy.	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	Main outcome is clinical improvement in the form of reduced pain and increased functional activity which is likely to be highly valued by most persons.[6]	
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the Comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	It is less clear if benefits of stem cell intervention outweigh the harms due to small to trivial benefit, based on limited evidence.	

Resources required How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No direct evidence of the resources required in stem cell transplantation in patients with tendinopathy was identified.	
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ● Moderate ○ High ○ No included studies	No research evidence was identified.	The GDG members were fairly certain that stem cell therapy requires large resources.
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○Favors the comparison ●Probably favors the comparison ○Does not favor either the intervention or the comparison ○Probably favors the intervention ○Favors the intervention ○Varies ○No included studies	No research evidence was identified.	The intervention was not found to be effective and hence the committee deferred to comment on cost effectiveness.
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○Reduced ●Probably reduced ○Probably no impact ○Probably increased ○Increased ○Varies ○Don't know	No research evidence was identified.	As stem cell therapy is an expensive treatment offered only at tertiary care centers, it is likely to increase inequity as it would not be affordable by all.
Acceptability Is the intervention acceptable to key stakeholders?		

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○No ○Probably no ●Probably yes ○Yes ○Varies ○Don't know	Despite uncertainty regarding the medical risks and benefits associated with stem cell injections, patients with tendinopathy have very high expectations from stem cell therapy.[7]	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○No ○Probably no ●Probably yes ○Yes ○Varies ○Don't know	No research evidence was identified. Stem Cell transplantation can be performed only in tertiary care centers so feasibility in lesser equipped hospitals and clinics is not possible.	Feasible to implement in tertiary centres.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE	**Trivial**	Small	Moderate	Large		Varies	Don't know

	JUDGEMENT						
EFFECTS							
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	**Moderate**	High			No included studies
COST EFFECTIVENESS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	**Use only in the context of rigorously conducted RCTs**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	●	○	○	○

CONCLUSIONS

Recommendation

Stem cell therapy is **not recommended** in routine practice for the treatment of tendinopathy. It may be used only in the context of rigorously conducted randomized controlled trials.

Justification

This recommendation has been made as there is very low certainty evidence of trivial reduction in pain and no improvement in function. There is little or no difference in undesirable effects between stem cell therapy and usual care. In addition, the follow up period is limited to comment on the long-term safety of stem cell therapy. Results should be interpreted with caution, in view of various study limitations like small number of participants and/or events, risk of bias and different sources of stem cell used.

vii. Data extraction:

Data extraction method

Three reviewers independently assessed the articles for possible inclusion in this systematic review. Any disagreement between the reviewers was resolved in consensus by mutual discussion or in consultation with the fourth reviewer. Data for trial design, study population, intervention details like the total number of intervention groups and comparisons made, number of participants in each intervention group, and outcome and time points of measurement were collected in prespecified format by two independent reviewers and disagreement were resolved in consultation with a third reviewer. Data were usually present as pre-intervention and post-intervention values; thus, post-intervention values were extracted for analysis of continuous outcome measures. In few cases, change scores with 95% CI were mentioned by the authors of individual study, and for those studies change scores were included. Data

represented in the plots were interpreted using WebPlotDigitizer. While extracting data for VAS, the mean and standard deviation were divided by 10 for the study by Randelli et al to convert the VAS to a 0-10 scale.

Risk of bias assessment

Three reviewers assessed the risk of bias of each trial in accordance with the Risk of Bias 2 (RoB) tool in the domains of bias arising from the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result as outlined in Cochrane Handbook for Systematic Reviews of Interventions. The risk of bias for the individual domain of each study was categorized into low, some concerns, or high based on the signalling questions for each domain. The overall risk of bias was determined based on the risk of bias from individual domains. If an agreement could not be made opinion from a fourth reviewer was sought.

Measurement of treatment effect

The primary outcome measure for the study was the pooled mean difference of change in severity of pain between intervention and comparator groups as determined by a change in the visual analog scale for pain rated on a scale of 1-10. We intended to report the overall effect estimate for adverse effects as an odd's ratio. We intended to present pooled mean differences for other secondary outcome measures like ASES, VISA and Constant score.

Assessment of heterogeneity

Clinical heterogeneity was clinically assessed by comparing important participant and intervention factors. Statistical heterogeneity was evaluated using Chi and I values. For value of I was less than 50%, a fixed effect model was used. By reviewing the PICO of each study, cause of heterogeneity was examined if value of I was more than 50%. If the heterogeneity could be explained by the differences in the PICO, subgroup analyses (by groups based on the different populations/interventions/outcomes) would be done and results would be provided for the same. However, if there were no critical differences in the PICO, the random-effects model was used to pool the results of all the included studies. Meta-regression was planned for the primary outcome measure with duration of the study as the predictor variable.

Assessment of reporting bias

Reporting bias was evaluated using the RoB2 tool by the Cochrane Collaboration. We intended to evaluate the outcome using the Outcome Reporting Bias in Trials (ORBIT) classification if any reporting bias was suspected in any trial. Publication bias was assessed using the symmetry of the funnel plot as well as Egger's regression.

Data synthesis

A random effect meta-analysis was used to synthesize data for the primary outcome measure of change in VAS score for pain. We intended to perform subgroup analysis for the type of tendinopathy (weight-bearing or non-weight-bearing), type of stem cell used, and type of comparator used in the included RCTs. Meta package in R studio integrated development environment using R version 4.2.3 was availed for synthesizing data in this meta-analysis.

Summary of findings and quality of evidence

Using the GRADE criteria for research limitations, consistency of effect, imprecision, indirectness, and publication bias, we assessed the quality of the evidence. The evidence was downgraded by one level if we thought the limitation was serious, and by two levels if we thought it was extremely serious. When a dose-response effect or a significant treatment impact is shown without any clear biases the evidence could also be upgraded under the GRADE method.

Data extraction Sheet:

Study	Chun et al. 2022[1]
Study type:	Randomized placebo-controlled trial
Number of participants:	23
Countries and setting:	Republic of Korea (Seoul National University Hospital)
Duration of study Follow up (post intervention):	24 months
Method of assessment of disease condition:	History of shoulder pain, examining the range of motion of the shoulder, performing empty can tests. Ultrasonographic findings and subsequent magnetic resonance imaging (MRI).
Subgroup analysis within study	None
Inclusion criteria:	• 18 years of age • Persistent shoulder pain lasting more than 3 months despite conservative treatment, with clinical findings compatible with partial tear of the supraspinatus tendon. • Positive empty can tests, • Decreased elevation/internal rotation of the arm with preserved external rotation in physical examinations

	• Hypoechoic lesions in the supraspinatus tendon not involving the full thickness of the tendon in the ultrasonographic examination later verified by MRI.
Exclusion criteria:	• Steroid injection within 6 weeks before initial evaluation Limited range of motion in multiple directions, including external rotation to rule out adhesive capsulitis; full-thickness tears of the supraspinatus tendon; symptomatic calcification of the tendon; arthritis; neurogenic atrophy around the shoulder; a history of proximal humeral fracture; or infectious diseases of the affected shoulder; Symptomatic bilateral rotator cuff tears, generalized pain syndrome, Ipsilateral radiculopathy, systemic inflammatory diseases, neurological conditions that may affect the assessment. • Bovine-derived protein allergy • Contraindications to MRI.
Recruitment/selection of patients:	Twenty-six candidates were eligible to participate after the screening. One declined to participate, and another had incompatible MRI findings. The remaining 24 participants were allocated to the three groups. One patient in the stem cell group withdrew after the entire injection procedure was prepared, right before the intervention. At the end of the study, 23 patients were included in the analyses.
Intervention: Type of stem cells with method of their characterization, Route of administration, Dose	The intervention group received commercial allogenic adipose tissue-derived adult MSC (Anterogen, Seoul) with fibrin glue as scaffold. All participants received an intra-lesional injection guided by ultrasonography. The manufactured stem cells were characterized by their cluster of differentiation (CD) cell surface markers. They expressed stromal cell-associated markers (CD10, CD13, CD29, and CD 90), but were negative for hematopoietic/bone marrow-derived stem cell markers (CD34, CD45, and Stro-1). Assessments of cell appearance, viability, identification, purity, content, and potency showed that the cells composed the lot release testing. The minimum criteria for release were as follows: 80% viability and less than 1% of cells expressing CD45. Potency and genomic stability were assessed by viable cell counting and karyotyping.

Outcomes reported with time points	• VAS (Baseline, 6 weeks, 12 weeks, 6, 12 and 24 months) • ASES (Baseline, 6 weeks, 12 weeks, 6, 12 and 24 months) • MRI: tear size (Improved/No change) [3 months, 1 year] • Adverse events (2 weeks, 6 weeks, 12 weeks, 6, 12 and 24 months)
Funding	Ministry of Health &Welfare, Republic of Korea and National Research Foundation (Korean Govt)
RoB2 Assessment: Specify separately for each domain	D1: Some concerns D2: Low D3: Low D4: Low D5: Low Overall: Some concerns

Study	Rodas et al. 2021[2]
Study type:	Randomized double blind active controlled trial
Number of participants:	20
Countries and setting:	Spain (Centro Medico Teknon Hospital, Barcelona)
Duration of study Follow up (post intervention):	6 months
Method of assessment of disease condition:	The lesion was confirmed by magnetic resonance imaging (MRI) of the patellar tendon in T2-weighted gradient echo, T2-weighted proton density fat saturation, and T2-weighted mapping sequences
Subgroup analysis within study	None
Inclusion criteria:	• Male participants aged between 18 and 48. • Pain and tenderness at the area of attachment of the patellar tendon on the lower pole of the patella for more than 4 months, with no clinically relevant response after conservative treatments. • US confirming disruption ≥ 3 mm of the fibrillar structure in the proximal portion of the patellar tendon, tendon thickening and a hypoechoic injury MRI of the patellar tendon in T2 FAT SAT sequence (fat saturation) showing an increase of ≥ 3 mm in longitudinal diameter at the proximal insertion.

	• Informed signed written consent by the participant. • The participant is able to understand the nature of the study.
Exclusion criteria:	• Participant younger than 18 (or legally dependent) or over 48 years of age. • MRI with a grade III–IV osteochondral lesion in any compartment of the knee. • Injury to the anterior or posterior cruciate ligament. • Local injection with corticosteroid during the previous 12 months. • Local injection with PRP during the previous 6 months. • Evidence of local or systemic infection. • Patients presenting with positive serology to HIV 1 or 2, hepatitis B (HBsAg, HBcAc), hepatitis C (anti-HCV-Ab) and syphilis. • Congenital or acquired conditions involving malformation and/or significant deformation of the knee that hampers the administration of the planned intervention and evaluation of the results. • Body mass index (BMI) greater than 30.5 (obesity grade II). • Active neoplastic disease. • Immunosuppression. • Simultaneous participation in another clinical trial or treatment with another research product during the 30 days prior to inclusion in the study. • Other pathologies or circumstances that may compromise participation in the study according to medical criteria.
Recruitment/selection of patients:	• Thirty-two patients were screened for eligibility. Out of which, 12 participants were excluded as 4 of them were >48 years of age, another 4 did not consent to participate, and the rest 4 had received previous interventions.
Intervention: Type of stem cells with method of their characterization, Route of administration, Dose	Autologous Expanded Bone Marrow Mesenchymal Stem Cells ($20x10^6$ cells) were administered in the patellar tendon. • In addition to quality-control tests (Mycoplasma negative), endotoxin levels were < 0.5 IU/mL, and flow cytometric immunophenotypic profiles were determined at this stage (CD14–, CD34–, CD45–, HLA-DR–, CD1051, CD1661, CD731, CD901). The antigenic profile conformed to the ISCT criteria for MSCs.
Outcomes reported with time points	• VAS • VISA-P • UTC

	• USG • MRI • Adverse events • All were assessed at baseline and 6 months
Funding	Institute de TerapiaRegenerativa Tissular in Medical Centre Teknon Hospital of Barcelona
RoB2 Assessment: Specify separately for each domain	D1: Some concerns D2: Low D3: Low D4: Low D5: Low Overall: Some concerns

Study	Rosario et al. 2021[3]
Study type:	Randomized controlled trial
Number of participants:	40
Countries and setting:	Brazil (Hospital Universitário Professor Edgard Santos)
Duration of study Follow up (post intervention):	6 months
Method of assessment of disease condition:	NMR and USG
Subgroup analysis within study	None
Inclusion criteria:	• Aged between 18 and 73 years. • Both sexes. • Clinical and radiological diagnosis (NMR and USG) of gluteal tendinopathy. Willing to participate in the study.
Exclusion criteria:	• Presenting infection at the surgical site. Comorbidities and contraindications for the surgical procedure.
Recruitment/selection of patients:	• Not mentioned, 48 patients were evaluated; out of which, 8 were lost to follow-up, and thus, 40 were included in the study.

Intervention: Type of stem cells with method of their characterization, Route of administration, Dose	Bone marrow mesenchymal stem cells; Cell counting and viability assessment were performed using a small cells suspension at the procedure site. Live cells were sampled by anti-CD34 antibody staining and Propidium Iodide incorporation. Using an ultrasound-guided standard 10-mL syringe, 20 mL of the solution with BMAC was injected in the gluteal tendon footprint.
Outcomes reported with time points	• VAS • EmoQoL • Lequesne • All outcomes assessed at baseline and 6 months.
Funding	Not specified
RoB2 Assessment: Specify separately for each domain	D1: Some concerns D2: High D3: High D4: High D5: Low Overall: High

viii. List of excluded studies:

S.No.	Study and location	Study Design
1.	Hernigou et al. 2014 France	Case control study
2.	Kim et al. 2017 Republic of Korea	Cohort study
3.	Kim et al. 2018	Prospective, non-randomized comparative, single-blind study
4.	Jo et al. 2018	Dose comparison study

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6. Ayers DC, Bozic KJ. The importance of outcome measurement in orthopaedics. Clinical Orthopaedics and Related Research®. 2013 Nov; 471:3409-11.
7. Puzzitiello RN, Dubin J, Menendez ME, Moverman MA, Pagani NR, Drager J, Salzler MJ. Public opinion and expectations of stem cell therapies in orthopaedics. Arthroscopy: The J Arthroscopic and Related Surgery. 2021 Dec 1; 37(12):3510-7.

5. NON-UNION OF BONE

i. **Key question in PICO format**

ii. **Search strategy**

iii. **PRISMA flow diagram**

iv. **Summary of included studies**

v. **Classification of studies based on level of stem cell manipulation**

vi. **Evidence to decision framework**

vii. **Data extraction**

viii. **List of excluded studies**

i. Key question in PICO format:

Population: Patients with Non-union of bone
Intervention: Any Stem cell and product derived from stem cells
Comparator: Usual Care/Conventional Care
Critical Outcomes: Efficacy: Reduction in pain, Disability; Safety: Severe Adverse Events

ii. Search strategy (September 2023):

Details of database searches:

Table 1: Database: **Embase**

S. No.	Keywords	Results
1.	'stem cell' OR 'stem cell'/exp OR 'stroma cell':ti,ab,kw OR 'stem cell':ti,ab,kw OR 'stroma cell'/exp OR 'stromal vascular fraction' OR 'stromal vascular fraction'/exp OR 'stem cell'/exp/mj OR 'stem cell niche'/exp OR 'stem cell niche':ti,ab,kw OR 'stem cells':ti,ab,kw OR stemcell:ti,ab,kw OR stemcells:ti,ab,kw	838304
2.	'stem cell transplantation' OR 'stem cell transplantation'/exp OR 'stem cell transplantation':ti,ab,kw OR 'mesenchymal stem cell transplantation'/exp OR 'cell therapy'/exp OR 'cell therapy':ti,ab,kw OR 'peripheral blood stem cell transplantation'/exp OR 'peripheral blood stem cell transplantation':ti,ab,kw OR 'peripheral blood stem cell'/exp OR 'peripheral blood stem cells':ti,ab,kw OR 'progenitor cell':ti,ab,kw OR 'mononuclear cell'/exp OR 'mononuclear cell':ti,ab,kw OR 'cord blood stem cell transplantation'/exp OR 'cord blood stem cell transplantation':ti,ab,kw OR 'cord blood stem cell'/exp OR 'cord blood stem cell':ti,ab,kw OR 'cord blood stem cells':ti,ab,kw	1484105
3.	'mesenchymal stem cell' OR 'mesenchymal stem cell'/exp OR 'mesenchymal stem cells':ti,ab,kw OR 'mesenchymal stroma cell':ti,ab,kw OR 'mesenchymal stromal cell therapy'/exp OR ('mesenchymal stromal cell'/exp)OR 'adipose derived stem cell'/exp OR 'adipose stem cells':ti,ab,kw OR 'adipose stem cell':ti,ab,kw OR 'adipose derived stem cells':ti,ab,kw OR 'induced pluripotent stem cell'/exp OR 'induced pluripotent stem cell transplantation'/exp OR 'induced pluripotent stem cells':ti,ab,kw OR 'totipotent stem cell'/exp OR 'totipotent stem cells':ti,ab,kw OR 'multipotent stem cell'/exp OR 'multipotent stem cells':ti,ab,kw OR 'pluripotent stem cell'/exp OR 'pluripotent stem celltransplantation'/exp OR 'pluripotent stem cells':ti,ab,kw	190280
4.	'human embryonic stem cell'/exp OR 'human embryonic stem cell' OR 'embryonic stem cell'/exp OR 'embryonic stem cell transplantation'/exp OR 'embryonic stem cells':ti,ab,kw OR 'wharton jelly'/exp OR 'wharton jelly derived mesenchymal stem cell'/exp OR 'satellite cell'/exp OR 'satellite cells':ti,ab,kw OR 'lipoaspirate'/exp OR 'lipoaspiration'/exp OR 'cell therapy'/exp OR 'cell based therapy':ti,ab,kw OR 'cell transplantation'/exp	319721

5.	'umbilical cord stem cell' OR 'umbilical cord stem cell'/exp OR 'cord blood stem cell transplantation'/exp OR 'fetal stem cell'/exp OR 'fetal stem cells':ti,ab,kw OR 'umbilical cord stem cells':ti,ab,kw OR 'colony forming cell':ti,ab,kw OR	211508
6.	'hematopoietic stem cell transplantation'/exp OR 'hematopoietic stem cell'/expOR 'hematopoietic stem cells':ti,ab,kw OR 'hematopoietic stem cell therapy':ti,ab,kw OR 'hemangioblast'/exp OR 'myoblast'/exp OR 'blastomere'/exp OR 'fetus blood'/exp OR 'adipose tissue stem cell'/exp	
7.	'bone marrow stem cells' OR 'bone marrow aspiration'/exp OR 'bone marrow aspirate':ti,ab,kw OR 'bone marrow aspirate concentrate'/exp OR 'bone marrow cell'/exp OR 'bone marrow cell transfer':ti,ab,kw OR 'colony forming unit'/exp OR 'epiblast stem cell'/exp OR polyblast:ti,ab,kw OR 'cord blood hematopoietic stem cell extract':ti,ab,kw OR 'hemacord'/exp OR 'remestemcel l':ti,ab,kw	213692
8.	'stem cell'/exp OR 'stem cell' OR allocord:ti,ab,kw OR ducord:ti,ab,kw OR autotemcel:ti,ab,kw OR azficel:ti,ab,kw OR skysona:ti,ab,kw OR 'elivaldogeneautotemcel'/exp OR temcell:ti,ab,kw OR stempeucel:ti,ab,kw	763000
9.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7	2115156
10.	('fracture nonunion'/exp OR 'fracture nonunion') OR 'fracture nonunion'/exp OR 'delayed union':ti,ab,kw OR 'fractures, ununited':ti,ab,kw OR 'ununited fracture':ti,ab,kw OR 'ununited fractures':ti,ab,kw OR 'pseudarthrosis'/exp OR 'bone nonunion':ti,ab,kw OR 'nonhealing fractures':ti,ab,kw OR 'nonhealing fracture':ti,ab,kw OR 'atrophic nonunion'/exp OR 'oligotrophic nonunion' OR 'hypertrophic nonunion':ti,ab,kwOR 'non-healing fracture':ti,ab,kw	33602
11.	'bone'/exp OR bone OR 'fracture'/exp OR fracture OR ('tibia'/exp OR tibia OR 'fibula'/exp OR fibula OR scaphoid OR 'spine'/exp OR spine OR 'rib'/exp OR rib OR 'radius'/exp OR radius OR 'ulna'/exp OR ulna OR 'femur'/exp OR femur OR 'metatarsal bone'/exp OR 'metatarsal bone' OR 'tarsal bone'/exp OR 'tarsal bone' OR 'talus'/exp OR talus)	2601809
12.	#8 AND #9 AND #10	1180
13.	'randomized controlled trial' OR 'randomized controlled trial'/exp OR ('randomized controlled trial'/exp AND topic) OR 'clinical trial'/exp OR 'clinical study'/exp OR 'observational study'/exp OR 'case control study'/exp OR 'cohort analysis'/exp OR 'cross- sectional study'/exp OR 'controlled clinical trial'/exp OR 'clinical trial' OR 'clinical trial'/exp OR 'controlled clinical trial'/expOR 'controlled study'/exp OR 'controlled trial, randomized':ti,ab,kw OR 'clinical study':ti,ab,kw OR 'phase 2 clinical trial'/exp OR 'phase 1 clinical trial'/exp OR 'phase 3 clinical trial'/exp OR 'phase 4 clinical trial'/exp	18558521
14.	#12 AND #13	659

Table 2: Database: **Pubmed**		
S.No.	**Keywords**	**Results**
1.	"stem cell"[All Fields] OR "stem cells"[MeSH Major Topic] OR "stem cells"[MeSH Terms] OR "stromal cells"[MeSH Terms] OR "stromal vascular fraction"[MeSH Terms] OR "stem cell niche"[MeSH Terms] OR "stemcell"[Title/Abstract] OR "stemcells"[Title/Abstract] OR "stroma cell"[Title/Abstract]	475520
2.	"stem cell transplantation"[Title/Abstract] OR "stem cell transplantation"[MeSH Terms] OR "cell transplantation"[MeSH Terms] OR "cell transplantation"[Title/Abstract] OR "cell therapy"[Title/Abstract] OR "peripheral blood stem cells"[MeSH Terms] OR "peripheral blood stem cells"[Title/Abstract] OR "peripheral blood stem cell transplantation"[Title/Abstract] OR "peripheral blood stem cell transplantation"[MeSH Terms] OR "progenitor cells"[Title/Abstract] OR "progenitor cell"[Title/Abstract] OR "mononuclear cell"[Title/Abstract] OR "mononuclear cells"[Title/Abstract] OR "cord blood stem cell transplantation"[Title/Abstract] OR "cord blood stem cell"[Title/Abstract] OR "cord blood stem cells"[Title/Abstract]	309319
3.	((((((((((((((((((((("mesenchymal stem cell"[Title/Abstract]) OR ("mesenchymal stem cells"[Title/Abstract])) OR ("mesenchymal stem cell transplantation"[MeSH Terms])) OR ("mesenchymal stem cells"[MeSH Terms])) OR ("mesenchymal stroma cell"[Title/Abstract])) OR ("mesenchymal stroma cells"[Title/Abstract])) OR ("mesenchymal stromal cell therapy"[Title/Abstract])) OR ("mesenchymal stromal cell transplantation"[Title/Abstract])) OR ("mesenchymal stromal cell"[Title/Abstract])) OR ("adipose derived stem cell"[Title/Abstract])) OR ("adipose stem cell"[Title/Abstract])) OR ("adipose stem cells"[Title/Abstract])) OR ("induced pluripotent stem cell"[Title/Abstract])) OR ("induced pluripotent stem cells"[MeSH Terms])) OR ("induced pluripotent stem cell transplantation"ns[Title/Abstract])) OR ("totipotent stem cells"[MeSH Terms])) OR ("multipotent stem cells"[MeSH Terms])) OR ("pluripotent stem cells"[MeSH Terms])) OR ("totipotent stem cell"[Title/Abstract])) OR ("totipotent stem cells"[Title/Abstract])) OR ("multipotent stem cell"[Title/Abstract])) OR ("multipotent stem cells"[Title/Abstract])) OR ("pluripotent stem cell"[Title/Abstract])) OR ("pluripotent stem cells"[Title/Abstract])	140092
4.	cells"[MeSH Terms])) OR ("embryonic stem cells/transplantation"[MeSH Terms])) OR ("embryonic stem cell transplantation"[Title/Abstract])) OR ("wharton jelly"[Title/Abstract])) OR ("wharton jelly"[MeSH Terms])) OR ("wharton jelly derived mesenchymal stem cells"[Title/Abstract])) OR ("satellite cells, perineuronal"[MeSH Terms])) OR ("satellite cells, skeletal muscle"[MeSH Terms])) OR ("satellite cell"[Title/Abstract])) OR ("lipoaspiration"[Title/Abstract])) OR ("lipoaspirate"[Title/Abstract])) OR ("cell based therapy"[Title/Abstract])	40376

5.	((((((((((("umbilical cord stem cell"[Title/Abstract]) OR ("umbilical cord stem cells"[Title/Abstract])) OR ("umbilical cord stem cell"[Title/Abstract])) OR ("umbilical cord stem cells"[Title/Abstract])) OR ("colony forming cells"[Title/Abstract])) OR ("hematopoietic stem cell transplantation"[Title/Abstract])) OR ("hematopoietic stem cell"[Title/Abstract])) OR ("hematopoietic stem cells"[Title/Abstract])) OR ("hematopoietic stem cell therapy"[Title/Abstract])) OR ("myoblasts"[MeSH Terms])) OR ("blastomeres"[MeSH Terms])) OR ("adipose tissue stem cell"[Title/Abstract])	69117
	((((((((((((((("bone marrow stem cells"[Title/Abstract]) OR ("bone marrow cells"[MeSH Terms])) OR ("bone marrow cells"[Title/Abstract])) OR ("bone marrow aspiration"[Title/Abstract])) OR ("bone marrow aspirate"[Title/Abstract])) OR ("bone marrow aspirate concentrate"[Title/Abstract])) OR ("bone marrow cell"[Title/Abstract])) OR ("bone marrow cell transfer"[Title/Abstract])) OR ("bone marrow cell transfusion"[Title/Abstract])) OR ("bone marrow cell transplant"[Title/Abstract])) OR ("bone marrow cell transplantation"[Title/Abstract])) OR ("colony forming unit"[Title/Abstract])) OR ("epiblast stem cell"[Title/Abstract])) OR ("epiblast stem cells"[Title/Abstract])) OR ("polyblast"[Title/Abstract])) OR ("cord blood hematopoietic cell extract"[Title/Abstract])) OR ("hemacord"[Title/Abstract])) OR ("remestemcell"[Title/Abstract])	219235
6.	((((("allocord"[Title/Abstract]) OR (ducord[Title/Abstract])) OR ("autotemcel"[Title/Abstract])) OR ("azficel"[Title/Abstract])) OR ("skysona"[Title/Abstract])	25
7.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7	757966
8.	((((((((((((((((((("fractures, bone"[MeSH Terms]) OR ("delayed union"[Title/Abstract])) OR ("fracture nonunion"[Title/Abstract])) OR ("fracture ununited"[Title/Abstract])) OR ("ununited fracture"[Title/Abstract])) OR ("ununited fractures"[Title/Abstract])) OR ("pseudoarthrosis"[Title/Abstract])) OR ("bone nonunion"[Title/Abstract])) OR ("bone nonunion fractures"[Title/Abstract])) OR ("nonhealing fracture"[Title/Abstract])) OR ("nonhealing fractures"[Title/Abstract])) OR ("atrophic nonunion"[Title/Abstract])) OR ("atrophic nonunion bone"[Title/Abstract])) OR ("atrophic nonunion fractures"[Title/Abstract])) OR ("atrophic nonunion cells"[Title/Abstract])) OR ("oligotrophic nonunion"[Title/Abstract])) OR ("oligotrophic nonunions"[Title/Abstract])) OR ("hypertrophic nonunion"[Title/Abstract])) OR ("hypertrophic nonunions"[Title/Abstract])) OR ("non healing fracture"[Title/Abstract])) OR ("non healing fractures"[Title/Abstract])	213169
9.	((((((((((((((((((("bone"[Title/Abstract]) OR ("tibia"[MeSH Terms])) OR ("tibia"[Title/Abstract])) OR ("fibula"[MeSH Terms])) OR ("fibula"[Title/Abstract])) OR ("scaphoid bone"[MeSH Terms])) OR ("scaphoid"[Title/Abstract])) OR ("spine"[MeSH Terms])) OR ("spine"[Title/Abstract])) OR ("rib"[Title/Abstract])) OR	1193286

	("rib"[Title/Abstract])) OR ("radius"[Title/Abstract])) OR ("radius"[MeSH Terms])) OR ("ulna"[MeSH Terms])) OR ("ulna"[Title/Abstract])) OR ("femur"[MeSH Terms])) OR ("femur"[Title/Abstract])) OR ("metatarsal bones"[MeSH Terms])) OR ("metatarsal"[Title/Abstract])) OR ("talus"[MeSH Terms])) OR ("talus"[Title/Abstract])) OR ("tarsal"[Title/Abstract])	
10.	#8 AND #9 AND #10	1311
11.	#11 AND Filters: Clinical Trial, Clinical Trial, Phase I, Clinical Trial, Phase II, Clinical Trial, Phase III, Clinical Trial, Phase IV, Comparative Study, Observational Study, Pragmatic Clinical Trial, Randomized Controlled Trial	92

Table 3: Database: **Web of Science**

S. No.	Keywords	Results
1.	((((((TI=("stem cell" OR "stem cells" OR "stemcell")) OR AB=("stem cell" OR "stem cells" OR "stemcell")) OR AK=("stem cell" OR "stem cells" OR "stemcell")) OR TS=('mesenchymal stem cell' OR 'mesen chymal stem cells' OR 'mesenchymal stem cell transplantation 'OR 'mesenchymal stem cell based therapeutics' OR "stem cell therapy" OR "stem cell transplantation therapy" OR "mesenchymal stem cell administration")) OR TI=('mesenchymal stem cell' OR 'mesenchymal stem cells' OR 'mesenchymal stem cell transplantation 'OR 'mesenchymal stem cell based therapeutics' OR "stem cell therapy" OR "stem cell transplantation therapy" OR "mesenchymal stem cell administration")) OR AB=('mesenchymal stem cell' OR 'mesenchymal stem cells' OR 'mesenchymal stem cell transplantation 'OR 'mesenchymal stem cell based therapeutics' OR "stem cell therapy" OR "stem cell transplantation therapy" OR "mesenchymal stem cell administration")) OR AK=('mesenchymal stem cell' OR 'mesenchymal stem cells' OR 'mesenchymal stem cell transplantation 'OR 'mesenchymal stem cell based therapeutics' OR "stem cell therapy" OR "stem cell transplantation therapy" OR "mesenchymal stem cell administration")	498013
2.	(((TS=("bone marrow derived mesenchymal stem cells" OR "bone marrow derived stem cell" OR "adipose derived stem cells" OR "adipose derived stem cell" OR "cord blood stem cell" OR "bone marrow derived mesenchymal stem cell")) OR TI=("bone marrow derived mesenchymal stem cells" OR "bone marrow derived stem cell" OR "adipose derived stem cells" OR "adipose derived stem cell" OR "cord blood stem cells" OR "bone marrow derived mesenchymal stem cell")) OR AB=("bone marrow derived mesenchymal stem cells" OR "bone marrow derived stem cell" OR "adipose derived stem cells" OR "adipose derived stem cell" OR "cord blood stem cell" OR "bone marrow derived mesenchymal stem cell")) OR AK=("bone marrow derived mesenchymal stem cells" OR "bone marrow derived stem cell" OR "adipose derived stem cells" OR "adipose derived stem cell" OR"bone marrow derived mesenchymal stem cell")	20732

3.	(((TS=("bone marrow aspiration" OR "bone marrow aspirate" OR "bone-marrow aspiration" OR "bone marrow aspirate")) OR TI=("bone marrow aspiration" OR "bone marrow aspirate" OR "bone-marrow aspiration" OR "bone marrow aspirate")) OR AB=("bone marrow aspiration" OR "bone marrow aspirate" OR "bone-marrow aspiration" OR "bone marrow aspirate")) OR AK=("bone marrow aspiration" OR "bone marrow aspirate" OR "bone-marrow aspiration" OR "bone marrow aspirate")	8062
4.	((TS=("mononuclear cell" OR "mononuclear cells" OR "mesenchymal stromal cell therapy" OR "induced pluripotent stem cell" OR "induced pluripotent stem cell transplantation" OR "induced pluripotent stem cells")) OR TI=("mononuclear cell" OR "mononuclear cells" OR "mesenchymal stromal cell therapy" OR "induced pluripotent stem cell" OR "induced pluripotent stem cell transplantation" OR "induced pluripotent stem cells")) OR AB=("mononuclear cell" OR "mononuclear cells" OR "mesenchymal stromal cell therapy" OR "induced pluripotent stem cell" OR "induced pluripotent stem cell transplantation" OR "induced pluripotent stem cells")	182356
5.	((TS=("stroma cell" OR "stroma cells" OR "stromal vascular fraction" OR "stem cell niche" OR "stem cell transplantation" OR "peripheral blood stem cell" OR "peripheral blood stem cell transplantation" OR "progenitor cell" OR "progenitor cells")) OR TI=("stroma cell" OR "stroma cells" OR "stromal vascular fraction" OR "stem cell niche" OR "stem cell transplantation" OR "peripheral blood stem cell" OR "peripheral blood stem cell transplantation" OR "progenitor cell" OR "progenitor cells")) OR AB=("stroma cell" OR "stroma cells" OR "stromal vascular fraction" OR "stem cell niche" OR "stem cell transplantation" OR "peripheral blood stem cell" OR "peripheral blood stem cell transplantation" OR "progenitor cell" OR "progenitor cells")	316797
6.	(((TS=("human embryonic stem cell" OR "embryonic stem cell" OR "embryonic stem cell" OR "wharton jelly" OR "wharton jelly derived mesenchymal stem cell" OR "satellite cell" OR "satellite cells" OR lipoaspirate OR lipoaspiration OR "cell therapy" OR "cell based therapy" OR "cell transplantation")) OR TI=("human embryonic stem cell" OR "embryonic stem cell" OR "embryonic stem cell" OR "wharton jelly" OR "wharton jelly derived mesenchymal stem cell" OR "satellite cell" OR "satellite cells" OR lipoaspirate OR lipoaspiration OR "cell therapy" OR "cell based therapy" OR "cell transplantation")) OR AB=("human embryonic stem cell" OR "embryonic stem cell" OR "embryonic stem cell" OR "wharton jelly" OR "wharton jelly derived mesenchymal stem cell" OR "satellite cell" OR "satellite cells" OR lipoaspirate OR lipoaspiration OR "cell therapy" OR "cell based therapy" OR "cell transplantation")) OR AK=("human embryonic stem cell" OR "embryonic stem cell" OR "embryonic stem cell" OR "wharton jelly" OR "wharton jelly derived mesenchymal stem cell" OR "satellite cell" OR "satellite cells" OR lipoaspirate OR lipoaspiration OR "cell therapy" OR "cell based therapy" OR "cell transplantation")	287002

7.	(((TS=("umbilical cord stem cell" OR "cord blood stem cell transplantation" OR "fetal stem cell" OR "fetal stem cells" OR "colony forming unit" OR "epiblast stem cell" OR "polyblast" OR "hematopoietic stem cell" OR "hematopoietic stem cells")) OR TI=("umbilical cord stem cell" OR "cord blood stem cell transplantation" OR "fetal stem cell" OR "fetal stem cells" OR "colony forming unit" OR "epiblast stem cell" OR "polyblast" OR "hemangioblast" OR "myoblast" OR "blastomere" OR "hematopoietic stem cell" OR "hematopoietic stem cells")) OR AB=("umbilical cord stem cell" OR "cord blood stem cell transplantation" OR "fetal stem cell" OR "fetal stem cells" OR "colony forming unit" OR "epiblast stem cell" OR "polyblast" OR "hemangioblast" OR "myoblast" OR "blastomere" OR "hematopoietic stem cell" OR "hematopoietic stem cells")) OR AK=("umbilical cord stem cell" OR "cord blood stem cell transplantation" OR "fetal stem cell" OR "fetal stem cells" OR "colony forming unit" OR "epiblast stem cell" OR "polyblast" OR "hemangioblast" OR "myoblast" OR "blastomere" OR "hematopoietic stem cell" OR "hematopoietic stem cells") "hemangioblast" OR "myoblast" OR "blastomere" OR	194236
8.	(((TS=("hemacord" OR "allocord" OR "duocord" OR "prochymal" OR "azficel" OR "omisirge" OR "SKYSONA" OR "elivaldogeneautotemcel" OR "stratagraft" OR "cartistem" OR "temcell" OR "stempeucel")) OR TI=("hemacord" OR "allocord" OR "duocord" OR "prochymal" OR "azficel" OR "omisirge" OR "SKYSONA" OR "elivaldogeneautotemcel" OR "stratagraft" OR "cartistem" OR "temcell" OR "stempeucel")) OR AB=("hemacord" OR "allocord" OR "duocord" OR "prochymal" OR "azficel" OR "omisirge" OR "SKYSONA" OR "elivaldogeneautotemcel" OR "stratagraft" OR "cartistem" OR "temcell" OR "stempeucel")) OR AK=("hemacord" OR "allocord" OR "duocord" OR "prochymal" OR "azficel" OR "omisirge" OR "SKYSONA" OR "elivaldogeneautotemcel" OR "stratagraft" OR "cartistem" OR "temcell" OR "stempeucel")	67
9.	#7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1	868986
10.	(((TS=("fracture nonunion" OR "delayed union" OR "fractures ununited" OR "ununited fractures" OR "ununited fracture" OR "pseudoarthrosis" OR "bone nonunion" OR "nonhealing fracture" OR "nonhealing fractures" OR "atrophic nonunion" OR "oligotrophic nonunion" OR "hypertrophic nonunion" OR "nonunion" OR "non-union" OR "non union" OR "delayed union" OR "delayedunion")) OR TI=("fracture nonunion" OR "delayed union" OR "fractures ununited" OR "ununited fractures" OR "ununited fracture" OR "pseudoarthrosis" OR "bone nonunion" OR "nonhealing fracture" OR "nonhealing fractures" OR "atrophic nonunion" OR "oligotrophic nonunion" OR "hypertrophic nonunion" OR "nonunion" OR "non-union" OR "non union" OR "delayed union" OR "delayedunion")) OR AB=("fracture nonunion" OR "delayed union" OR "fractures ununited" OR "ununited fractures" OR "ununited fracture" OR "pseudoarthrosis" OR "bone nonunion" OR "nonhealing fracture" OR "nonhealing fractures" OR "atrophic nonunion" OR "oligotrophic nonunion" OR "hypertrophic nonunion" OR "nonunion" OR "non-union" OR "non union" OR "delayed union" OR "delayedunion")) OR AK=("fracture nonunion" OR "delayed	20075

	union" OR "fractures ununited" OR "ununited fractures" OR "ununited fracture" OR "pseudoarthrosis" OR "bone nonunion" OR "nonhealing fracture" OR "nonhealing fractures" OR "atrophic nonunion" OR "oligotrophic nonunion" OR "hypertrophic nonunion" OR "nonunion" OR "non-union" OR "non union" OR "delayed union" OR "delayedunion")	
11.	(((TS=("bone" OR "fracture" OR "tibia" OR "fibula" OR "scaphoid" OR "spine" OR "rib" OR "radius" OR "ulna" OR "femur" OR "tarsal" OR "tarsal bone" OR "talus")) OR TI=("bone" OR "fracture" OR "tibia" OR "fibula" OR "scaphoid" OR "spine" OR "rib" OR "radius" OR "ulna" OR "femur" OR "tarsal" OR "tarsal bone" OR "talus")) OR AB=("bone" OR "fracture" OR "tibia" OR "fibula" OR "scaphoid" OR "spine" OR "rib" OR "radius" OR "ulna" OR "femur" OR "tarsal" OR "tarsal bone" OR "talus")) OR AK=("bone" OR "fracture" OR "tibia" OR "fibula" OR "scaphoid" OR "spine" OR "rib" OR "radius" OR "ulna" OR "femur" OR "tarsal" OR "tarsal bone" OR "talus")	2813775
12.	TS=(("randomized controlled trial") OR ("controlled clinical trial") OR ("clinical trial") OR ("clinical study") OR ("observational study") OR ("case control study") OR ("cohort analysis") OR ("cross-sectional study") OR ("controlled clinical trial") OR ("cohort analysis") OR ("controlled study") OR ("controlled trial") OR ("phase 1 clinical trial") OR ("phase 2 clinical trial") OR ("phase 3 clinical trial") OR ("phase 4 clinical trial"))	1275945
13.	#9 AND #10 AND #11	900
14.	#13 AND #12	42

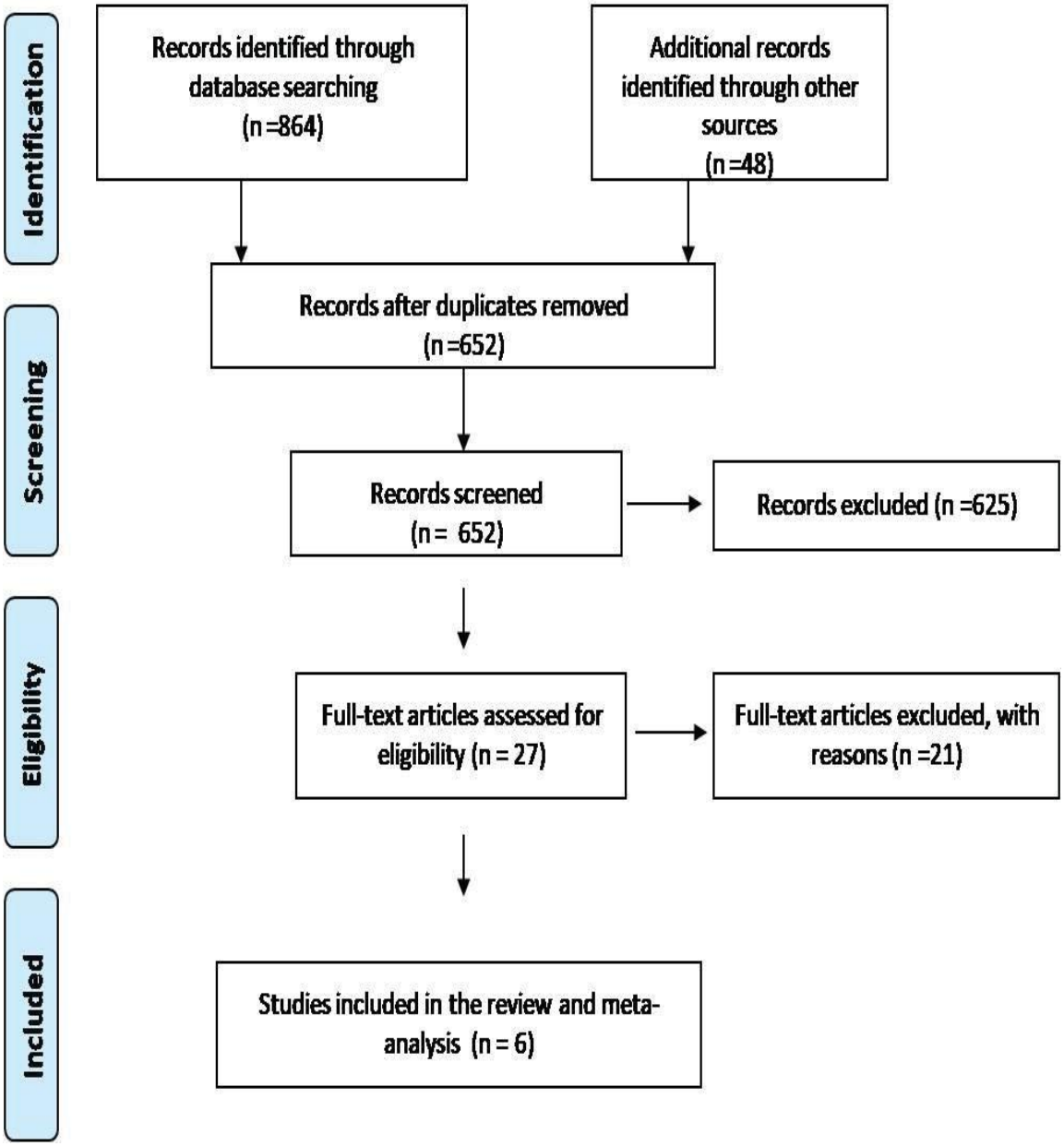
Table 4: Database**: Cochrane**

S. No.	Keywords	Results
1.	MeSH descriptor: [Stem Cells] explode all trees	1152
2.	MeSH descriptor: [Mesenchymal Stem Cells] explode all trees	284
3.	MeSH descriptor: [Stem Cell Transplantation] explode all trees	3193
4.	MeSH descriptor: [Bone Marrow Transplantation] explode all Trees	1622
5.	MeSH descriptor: [Cord Blood Stem Cell Transplantation] explode all trees	48
6.	MeSH descriptor: [Stromal Vascular Fraction] explode all trees	12
7.	MeSH descriptor: [Cell- and Tissue-Based Therapy] explode all Trees	8748
8.	MeSH descriptor: [Satellite Cells, Skeletal Muscle] explode all Trees	40
9.	MeSH descriptor: [Exosomes] explode all trees	28
10.	MeSH descriptor: [Secretome] explode all trees	3
11.	MeSH descriptor: [Bone Marrow Cells] explode all trees	1899
12.	MeSH descriptor: [Hematopoietic Stem Cells] explode all trees	368
13.	MeSH descriptor: [Hemangioblasts] explode all trees	1

14.	MeSH descriptor: [Blastomeres] explode all trees	38
15.	("stem-cells") OR ("stem cells") OR ("stem cell") OR ("mesenchymal stem cell") OR ("mesenchymal stem cells") (Word variations have been searched)	16220
16.	("mesenchymal stem cell-based therapies") OR ("mesenchymal stem cell-based therapy") OR ("mesenchymal stem cell administration") OR ("mesenchymal stem cell therapy") OR ("mesenchymal stem cell transplantation") (Word variations have been searched)	649
17.	("mesenchymal progenitor cell") OR ("mesenchymal stem cell-based therapeutics") OR ("mesenchymal stromal cells") OR ("stem cell transplantation") OR ("stem cell therapy") (Word variations have been searched)	11225
18.	("stem cell transplantation therapy") OR ("bone marrow derived stem cells") OR ("bone marrow derived mesenchymal cells") OR ("bone marrow aspirate") OR ("bone marrow aspiration") (Word variations have been searched)	965
19.	("stem cell transplant") OR ("bone marrow stem cell") OR ("bone- marrow stem cell") OR ("bone-marrow stem cells") OR ("cord blood stem cells") (Word variations have been searched)	10826
20.	("adipose-derived stem cell") OR ("adipose-derived stromal cell") OR (lipoaspirate) OR (lipoaspiration) OR (hemangioblast) (Word variations have been searched)	308
21.	(hemacord) OR (allocord) OR (duocord) OR (prochymal) OR (azficel) OR ("colony forming cells") (Word variations have been searched)	57
22.	(omisirge) OR (SKYSONA) OR ("elivaldogeneautotemcel") OR (stratagraft) OR (cartistem) (Word variations have been searched)	16
23.	(temcell) OR (stempeucel) OR ("epiblast stem cell") OR ("fetal stem cell") OR ("umbilical cord stem cell") (Word variations have been searched)	40
24.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23	23739
25.	(nonunion OR "non-union") OR nonunion OR non-union OR “non union” OR union OR delayed union OR delayedunion (Word variations have been searched)	7472
26.	("bone nonunion") OR ("bone non-union") OR ("bone nonunion fracture") OR ("bone non-union fractures") (Word variations have been searched)	60
27.	("nonunion fractures") OR ("non-union fractures") OR ("bone nonunion fractures") OR ("bone non-union fractures") (Word variations have been searched)	59
28.	("nonhealing fracture") OR ("nonhealing fractures") OR ("non- healing fracture") OR ("non-healing fractures") OR ("bone non- union fractures") (Word variations have been searched)	9

29.	("fracture nonunions") OR ("nonunion bone fracture") OR ("nonunion bone defect") OR ("non-union bone defect") OR ("fracture nonunion") (Word variations have been searched)	458
30.	("delayed union") OR ("non-union bone fracture") OR ("nonunion bone defects") OR ("non-union bone defects") OR ("nonunion delayed union") (Word variations have been searched)	225
31.	("non-union delayed union") OR ("oligotrophic nonunion") OR ("oligotrophic non-union") OR ("oligotrophic nonunions") OR ("hypertrophic nonunion") (Word variations have been searched)	12
32.	(pseudoarthrosis) OR ("atrophic nonunion") OR ("atrophic non- union") OR ("hypertrophic non-unions") OR ("hypertrophic nonunion") (Word variations have been searched)	116
33.	("atrophic nonunion fracture") OR ("atrophic non-unions") OR ("atrophic nonunions") OR ("atrophic non-union fracture") OR ("atrophic nonunion fractures") (Word variations have been searched)	17
34.	("nonhealing fracture") OR ("nonhealing fractures")OR ("non- healing fracture") OR ("atrophic non-union fractures") OR ("fracture non- union") OR ("fracture nonunion") OR ("non- healing fractures") (Word variations have been searched)	493
35.	(tibia OR fibula OR scaphoid OR spine OR rib OR radius OR ulna OR femur OR tarsal OR metatarsal OR talus OR bone OR fracture)	106258
36.	#25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34	7543
37.	#36 AND #35	2539
38.	#24 AND #35 AND #36	8358
39.	#24 AND #37	171

iii. PRISMA flow diagram:



iv. Summary of included studies:

Study	Population	Intervention	Comparison	Outcomes	Comments
Hernigou et al. 2017[1]	Infected tibial non unions, with absence of healing for longer than 9 months, no observation of healing in previous three months. Infection confirmed by routine biologic (full blood count, CRP) and radiologic evidence of infection (sequestrum).	Antibiotic therapy protocol was the same (60 days) in the two groups. External fixation (internal osteosynthesis removed), debridment of bone and soft tissue was performed Bone graft (cancellous bone from iliac crest) supercharged with granulocytes precursors. Bone marrow concentrate was evaluated as CFU-F concentration.	Antibiotic therapy protocol was the same (60 days) in the two groups. External fixation (internal osteosynthesis removed), debridment of bone and soft tissue was performed. Standard bone graft (cancellous bone from iliac crest)	Non-union healing, Recurrence of infection, graft resorption, Number of procedures needed in each group	Excluded by committee as infected non union was the included population.

Zhai et al. 2016[2]	**Inclusion criteria:** Non-union of long bones as defined by "at least 6 months after the fracture but has not been healed yet and no further tendency of healing for 3 months is apparent". **Exclusion criteria:** Patients with disorder of coagulation or on anti-coagulant medication, local tumor, thrombosis (local), infected non-union, defect>1.5 cm, immature bone development, severe cardiovascular and cerebrovascular disease, severe malnutrition, pregnancy, local inflammation, heart disease, and fracture ends are active.	Autologous BMMC-ESWT (extracorporeal shock wave therapy), n=32. Bone marrow stem cells culture propagated till P3. The stem cells expressed CD44, CD90, CD105, but didn't express CD34, CD45 and CD14. Cell purity for hBMSC were >95%.	ESWT (n=31)	Quantity of callus formation at 3, 6, 9 and 12 months, Treatment failure.	Excluded by the committee as the assessment of bone union as evidenced from the representative images was not proper. The study was an add-on trial (all patients were given ESWT and bone marrow stem cells were used as only add-on. Although, number of internal fixations were similar in both the groups (22 in Gp A and 19 cases in Gp B), however details of internal fixation was not provided. Data not provided against type of non-union (atrophic, oligotrophic and hypertrophic).

Shirin Toosi 2023[3]	**Inclusion Criteria:** Adults without any other health issue, no prior surgical procedure with unilateral scaphoid waist non-union were included. Scaphoid non-union diagnosed on the basis of clinical (anatomic snuffbox tenderness) and imaging criteria (Radiography and CT scan). **Exclusion Criteria:** Pathologic fractures, bilateral wrist injury, previous surgical treatment, proximal or distal pole non-union, scaphoid nonunion advanced collapse (SNAC) type 3 or 4, existence of other associated fractures, diabetes, heavy smoker, hormone related issues, vascular diseases, steroid, immunosuppressant users.	Non-union site underwent decortication. Collagen/polyglycolic acid (CPGA)+cell therapy (BM-MSC). Bone marrow culture was extracted and MSC were cultured. BM-MSC were microscopically examined, as well as surface molecular markers were evaluated using flowcytometry for surface markers CD11b, CD34, CD44, CD45, CD90, CD73, and HLA-DR.	Non-union site underwent decortication. Autologous iliac crest bone graft standard therapy.	Union, Grip strength, pinch strength, Patient rated wrist evaluation questionnaire (PRWE), Quick disabilities of the arm, shoulder and hand questionnaire (QDASH), Mayo wrist score, range of motion.	Excluded by the committee as scaphoid non-nion is a completely distinct entity, which is different from long union of long bones. AVN was seen in one of the images. Follow period was less.

Zhang et al. 2018[4]	**Inclusion Criteria:** Tibial non-union (radiographically confirmed tibial non-union), between 18-50 years, non-union gap between 3-12 cm. **Exclusion Criteria:** >50 years, pregnant or planning for pregnancy, pacemaker, cancer, peripheral vascular disease, diabetes	Ilizarove+Intraosseous injection of autologous mesenchymal stem cell (n=13). Extracted bone marrow was transferred through commercially available MSC extractor. MSC harvest was $72x10^6$ total nucleated cells/ml	Ilizarovprocedure alone (n=12).	Occurrence of stable union. Time in hospital (months), Time taken to union (months), Duration of external fixation, External fixation index.	Excluded, as stem cell characterization was not proper.
Bajada et al. 2008[5]	Twelve men with non-union [Four tibial and 8 femoral non-union] resistant to multiple previous attempts of treatment (mean 3.75 procedure).	Non-union site underwent decortication. BMSSC was added to the synthetic bone substitute on one side of fracture (Medial or larteral) according to randomization. (N=12 side). Bone marrow aspiration and MSC culture. BM-MSCs were culture expanded to an average of $5x10^6$ cells.	Non-union site underwent decortication. The other side of non-union served as control (received only synthetic bone substitute). (N=12 side)	Standard radiographs were taken and evaluated independently by three experienced musculoskeletal radiologists, The extent of callus formation was recorded. In equivocal cases CT was also done.	Excluded, as stem cell characterization was not proper.

Yuan et al. 2006[6]	Bone non-union and bone defection cases. One forty patients with humeral and tibial fractures (all 6-8 months after surgery) were included, Male:76 males Female: 64	Surgical exposure of the fractured end, removal of local callus, biting off the sclerotic bone at both ends of the fracture, opening of the medullary cavity, and reduction using conventional fixation methods. Iiliac bone harvesting was done to create thin strips/blocks, which was incorporated around the fracture/defect sites. (n=70). Bone marrow aspiration and MSC culture. BM-MSCs were culture expanded to an average of $5x10^6$ cells.	Surgical exposure of the fractured end, removal of local callus, biting off the sclerotic bone at both ends of the fracture, opening of the medullary cavity, and reduction using conventional fixation methods. Bone matrix with bone marrow (n=70).	Callus formation, Fracture healing time, Safety	Excluded, as stem cell characterization was not proper.

v. Classification of studies on the basis of level of manipulation of the stem cell/ Stem cell derived product used (*interpreted by the Secretariat as defined by CDSCO* and the information provided in the trial itself*):

S. No.	Trial Details	Intervention	Level of manipulation	Information extracted from trial
1.	Toosi et al. 2023	BM-MSC	More	*"Under local anesthetics, the orthopedic surgeon aspirated about 60 mL of bone marrow from the posterior iliac crest of patients in the case group. MSC culture was conducted."*

* as defined by CDSCO in Annexure- I of the guideline document

vi. Evidence to decision framework:

QUESTION

What is the efficacy and safety of Stem Cell Therapy compared to standard care in patients with Non-union of Bone?	
POPULATION:	Non-union of Bone
INTERVENTION:	Any Stem cell and product derived from stem cells
COMPARISON:	Usual Care/ Conventional Care in treatment of nonunion of bone
MAIN OUTCOMES:	Reduction in pain and disability; Serious adverse event
SETTING:	Hospital/Tertiary Care setting
PERSPECTIVE:	Population
BACKGROUND:	Non-union of bone following fracture is an orthopedic condition with a high morbidity and clinical burden. Despite its estimated global prevalence of nine million annually, the limit of bone regeneration therapy still results in patients living with pain, a reduced quality of life and associated psychological, social and financial repercussions. Despite the advances in the management of non-union that have been borne out of research and technology, there still exists an undefined consensus regarding the optimal management choice for the condition.
CONFLICT OF INTERESTS:	None

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○No ○Probably no ○Probably yes ●Yes ○Varies ○Don't know	When the healing process of a fractured bone fails owing to inadequate immobilization, failed surgical intervention, insufficient biological response or infection, the outcome after a prolonged period of no healing is defined as non- union. Non-union represents a chronic medical condition not only affecting function but also potentially impacting the individual's psychosocial and economic well-being.[7]	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○Trivial ○Small ○Moderate ○Large ○Varies ●Don't know	**QDASH:** Evidence from one RCT of 10 participants of scaphoid non-union reporting the QDASH (Quick disability of the arm, shoulder and hand) score at the end of 3 months showed a mean difference of -10.05 (95% CI: -18.28 to -1.82) between the stem cell therapy arm as compared to the usual care. The difference was statistically significant but about half of the MCID of 20, hence unimportant clinically. **Mayo wrist score:** Evidence from one RCT of 10 participants evaluated wrist functions (among participants with scaphoid fracture) following treatment with stem cell derived products and showed a mean difference of -4.00 (95% CI: -32.29 to 24.29). However, no statistically significant difference was seen between the two groups.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○Trivial ○Small ○Moderate ○Large	No severe adverse events were reported. The evidence is insufficient to draw firm conclusions due to limited long term follow up of the trial.	

○ Varies ● Don't know		

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The evidence in this review is of very low quality due to high risk of bias and imprecision in the effect shown by stem cell therapy.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	Main outcome is clinical improvement in the form of reduced pain and increased functional activity which is likely to be highly valued by most persons.[8, 9]	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	It is less clear if benefits of stem cell intervention outweigh the harms due to trivial benefit, based on limited evidence.	
Resources required How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No direct evidence of the resources required in stem cell transplantation in patients with non-union of bone was identified.	
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○Very low ○Low ●Moderate ○High ○No included studies	No research evidence was identified.	The GDG members were fairly certain that stem cell therapy requires large resource
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○Favors the comparison ●Probably favors the comparison ○Does not favor either the intervention or the comparison ○Probably favors the intervention ○Favors the intervention ○Varies ○No included studies	No research evidence was identified.	The intervention was not found to be effective and hence the committee deferred to comment on cost effectiveness.
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○Reduced ●Probably reduced ○Probably no impact ○Probably increased ○Increased ○Varies ○Don't know	No research evidence was identified.	As stem cell therapy is an expensive treatment offered only at tertiary care centers, it is likely to increase inequity as it would not be affordable by all.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○No ○Probably no ●Probably yes ○Yes ○Varies ○Don't know	Despite uncertainty regarding the medical risks and benefits associated with stem cell injections, patients with nonunion of bone have very high expectations from stem cell therapy.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○No ○Probably no ●Probably yes ○Yes ○Varies ○Don't know	No research evidence was identified. Stem Cell transplantation can be performed only in tertiary care centers so feasibility in lesser equipped hospitals and clinics is not possible.	Feasible to implement in tertiary centres.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	**Don't know**
UNDESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	**Don't know**
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the interventio n	Varies	Don't know
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	**Moderate**	High			No included studies
COST EFFECTIVENESS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the interventio n	Varies	No included studies

	JUDGEMENT						
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	**Use only in the context of rigorously conducted RCTs**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	●	○	○	○

CONCLUSIONS

Recommendation

Stem Cell Therapy is **not recommended** in routine practice for the treatment of non-union of bone. It may be used only in the context of rigorously conducted randomized controlled trials.

Justification

The evidence is inadequate in quantity and quality to determine the safety and efficacy of stem cell therapy in patients with non-union of bone. In addition, the follow up period is limited to comment on the side effect profile and long-term safety is not known. Results need to be interpreted with caution due to small number of participants and/or events, limited duration of follow up in the single study that evaluated the clinical and functional outcomes of Collagen/PGA Scaffolds and Cell-Based Therapy in scaphoid bone non unions.

vii. Data extraction:

Data extraction methods

Data was searched by two reviewers. Initially title and abstract screening was done followed by full text screening. In case of any discrepancy, it will be consulted with a third reviewer and the issue was resolved. Data extraction was done. The data collected were name of author and year of publication, type of research study, demographic features, how the diagnosis of non union was made, details of stem cell therapy, method of stem cell harvesting, any manipulation, technique of application of stem cell, pre-specified outcomes. After this, analysis of data was done.

In case of outcome data is present in two or more studies, we will conduct a meta-analysis for the same using RevMan, and open meta-analyst and R based platforms (e.g. metaphor package). In case of dichotomous data, relative risk (RR) was calculated with 95% confidence interval. In case of continuous data, mean difference with 95% confidence interval was calculated. I^2 was taken as a measure of heterogeneity. In case of high heterogeneity ($I^2 > 50\%$), a random effect model was used, else a fixed effect model was used. Subgroup analysis was conducted to explain heterogeneity.

Data extraction sheet

Study		Toosi et al. 2023[3]
Study type:		RCT
Number of participants:		N=10
Countries, setting and Funding:		Iran, Funding support by Mashhad University of Medical Sciences (MUMS) with project no. 951244.
Duration of study Follow up (post intervention):		3 months
Method of assessment of disease condition:		Considered both clinical (anatomical snuffbox tenderness) and radiography (serial radiography and confirmed by CT).
Subgroup analysis within study		Nil
Population	**Inclusion criteria:**	Adults without any other health issue, no prior surgical procedure with unilateral scaphoid waist non-union were included. Scaphoid non-union diagnosed on the basis of clinical (anatomic snuffbox tenderness) and imaging criteria (Radiography and CT scan) were included.
	Exclusion criteria:	Pathologic fractures, bilateral wrist injury, previous surgical treatment, proximal or distal pole nonunion, scaphoid non-union advanced collapse (SNAC) type 3 or 4, existence of other

		associated fractures, diabetes, heavy smoker, hormone related issues, vascular diseases, steroid, immunosuppressant users.
Recruitment/ selection of patients:		Patients were randomly assigned to either collagen/polyglycolic acid (CPGA) scaffold + cell therapy group or autologous iliac crest bone graft standard therapy group.
Intervention:	**Intervention details**	Non-union site underwent decortication. Collagen/polyglycolic acid (CPGA)+cell therapy (BM-MSC).
	Source and type of stem cells	60 ml of bone marrow was aspirated, MSC was separated (Ficoll-Hypaque gradient) and MSC culture was conducted.
	Method of their characterization	BM-MSC were microscopically examined, as well as surface molecular markers were evaluated using flowcytometry for surface markers CD11b, CD34, CD44, CD45, CD90, CD73, and HLA-DR.
	Route of administration	The MSCs were seeded to a collagen + polyglycolic acid scaffold. Scaffold was wetted in a cell suspension of 0.5 containing 2 million cells. Inter-segmental space was filled with three to four BM-MSC scaffolds.
	Dose	Scaffold was wetted in a cell suspension of 0.5 ml containing 2 million cells. Inter-segmental space was filled with three to four BM-MSC scaffolds.
	Dose - If the trial has taken multiple doses, then which dose values has been used	NA
Control arm treatment		Non-union site underwent decortication. Autologous iliac crest bone graft standard therapy.
Efficacy Outcomes reported with time points:		All outcomes were evaluated till three months following the procedure. The outcomes evaluated were Grip and pinch strengths, wrist function score, disability, range of motion and union rate using clinical and radiologic healing criteria.
Safety Outcomes reported with time points- Serious AE		No serious adverse event was reported by the authors during follow up (upto 3 months post procedure).
Safety Outcomes reported with time points- Other Adverse Events		No adverse event was reported by the authors during follow up (upto 3 months post procedure).

viii. List of excluded studies:

Article details	Reason for exclusion
Tang YF et al. 2020	• Population is delayed fracture healing • Comparison is different (percutaneous autologous bone marrow injection) vs (percutaneous autologous bone marrow injection + platelet rich plasma).
Zhang S et al. 2017	• Comparision: BM-MSC versus BMMSC + PRP
Thus et al. 2015	• Not RCT
Kim et al. 2009	• Included population is different (patient with fracture, not fracture nonunion)
Wang et al. 2013	• Not RCT
Gomez-Barrena et al. 2018	• Protocol
Weel et al. 2015	• Protocol
Rahman et al. 2021	• Delayed union population • Single group? • Full text could not be retrieved (Only abstract was used for evaluation)
Kuroda et al. 2023	• Single arm study • Historical control
Cheng et al. 2016	• Retrospective study
Wang et al. 2013	• Not RCT
Hedge et al. 2014	• Not RCT
Guadalupe et al. 2016	• Population is mandibular fracture (not mandibular fracture non-union)
Kuhota et al. 2017	• Different population (not a population with non union of bone). Rather population is patients undergoing posterolateral lumbar fusion.
Lee et al. 2014	• Population is not a population with non union of bone
Liebergall et al. 2013	• Population is delayed union
Mayerson et al. 2019	• Population is not a population with non union (rather population is patients undergoing subtalar arthrodesis)
Dallari et al. 2007	• Patients undergoing tibial osteotomy (not a patient population with non union)
Manneli et al. 2017	• Population different (fractures of atrophic mandibles) • Not RCT
Frutos et al. 2020	• Patients undergoing lumbar fission surgery
Shim et al. 2020	• Population is patients with osteoporotic vertebral fractures

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6. MENISCAL TEAR/ MENISCOPATHY

i. **Key question in PICO format**

ii. **Search strategy**

iii. **PRISMA flow diagram**

iv. **Summary of included studies**

v. **Evidence to decision framework**

vi. **Classification of studies based on level of stem cell manipulation**

vii. **Data extraction**

viii. **List of excluded studies**

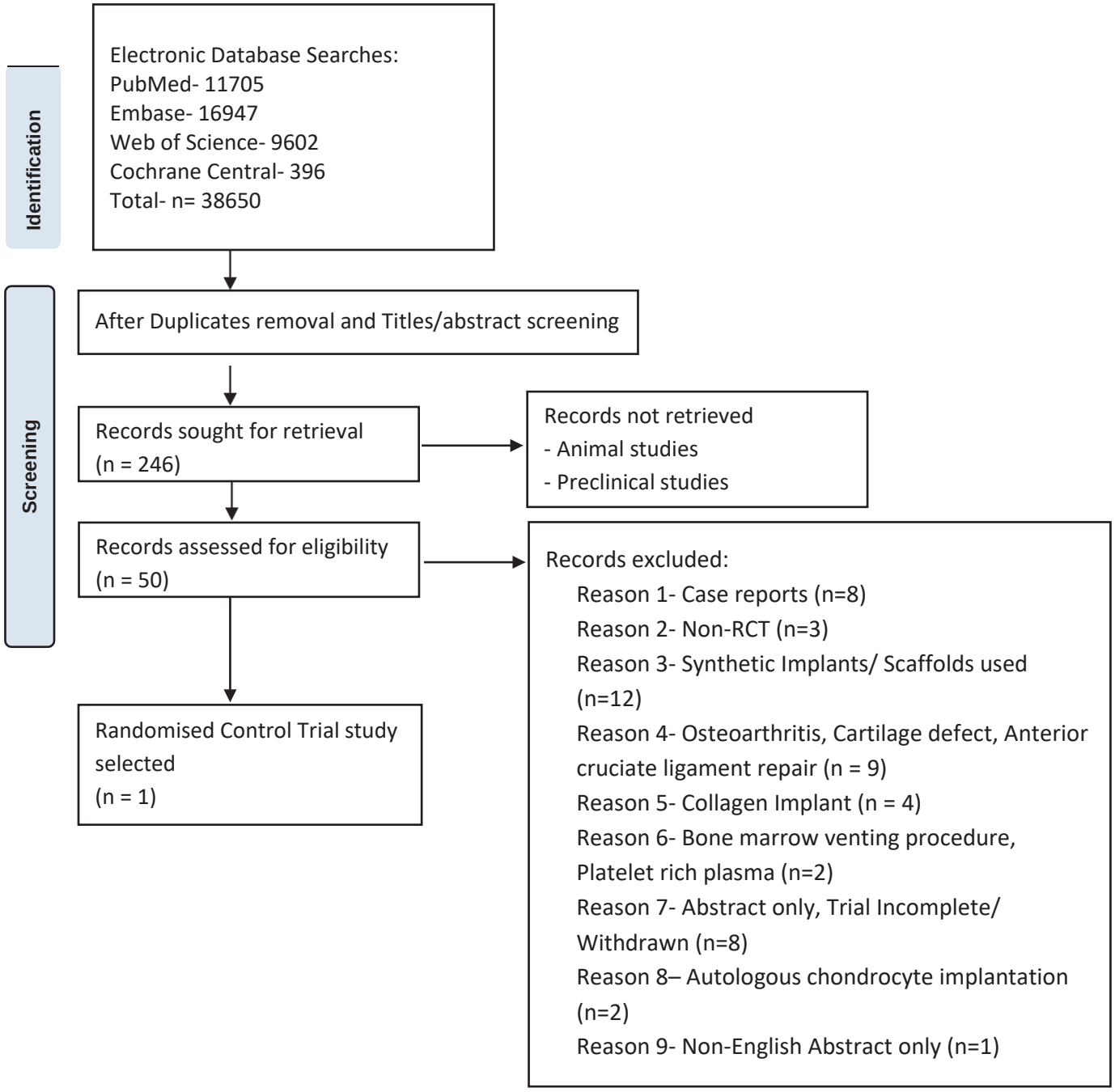
i. Key question in PICO format:

Population: Patients with meniscopathies
Intervention: Any Stem cell and product derived from stem cells
Comparator: Usual Care/ Conventional Care
Critical Outcomes: Efficacy: Reduction in pain, Disability; Safety: Severe Adverse Events

ii. Search strategy (September 2023):

Keyword	Pubmed	Embase	Web of Science	Cochrane Central (trials, reviews)
(Meniscus OR Meniscopathiesor meniscal repair or meniscal tear) and Stem Cells	561	1001	732	28,3
(Meniscus OR Meniscopathiesor meniscal repair or meniscal tear) and Mesenchymal Stem Cells	342	685	560	23
(Meniscus OR Meniscopathiesor meniscal repair or meniscal tear) and Synoviocytes	68	192	60	3
(Meniscus OR Meniscopathiesor meniscal repair or meniscal tear) and Bone Marrow Cells	157	454	252	11,2
(Meniscus OR Meniscopathiesor meniscal repair or meniscal tear) and Adipocytes	13	47	10	0
(Meniscus OR Meniscopathiesor meniscal repair or meniscal tear) and Chondrocytes	1221	2309	957	23,2
(Meniscus OR Meniscopathiesor meniscal repair or meniscal tear) and Blood Cells	176	820	140	15,8
(Meniscus OR Meniscopathiesor meniscal repair or meniscal tear) Cell and Culture	927	1029	634	8,4
(Meniscus OR Meniscopathiesor meniscal repair or meniscal tear) and Tissue Engineering	1082	2670	1403	10,1
(Meniscus OR Meniscopathiesor meniscal repair or meniscal tear) and Biologicals	2271	180	467	22,9
(Meniscus OR Meniscopathiesor meniscal repair or meniscal tear) and scaffolds	670	533	769	17,3
(Meniscus OR Meniscopathiesor meniscal repair or meniscal tear) and constructs	595	297	635	11,6
(Meniscus OR Meniscopathiesor meniscal repair or meniscal tear) and cells	2237	3927	2141	75,13
(Meniscus OR Meniscopathiesor meniscal repair or meniscal tear) and growth factors	949	430	568	15,4
(Meniscus OR Meniscopathiesor meniscal repair or meniscal tear) and regenerative medicine	398	676	274	4,1
(Meniscus OR Meniscopathiesor meniscal repair or meniscal tear) and implant	1155	1697	0	71,4

iii. PRISMA flow diagram:



iv. Summary of included studies:

Study	Population	Intervention	Comparison	Outcomes
Vangsness et al. 2014[1]	Patients for a partial medial Meniscectomy	Group A- Single intra-articular injection of 50 million human mesenchymal stem cells suspended in 2mL (20 mg) of sodium hyaluronate (hyaluronicacid/hyaluronan), human serum albumin (1.2%), and PlasmaLyte A to a volume of 5ml after partial meniscectomy. Group B- Single intra-articular injection of 150 million human mesenchymal stem cells suspended in 2mL (20mg) of sodium hyaluronate(hyaluronicacid/hyaluronan), human serum albumin (1.2%), and PlasmaLyte A to a volume of 5mL after partial meniscectomy.	Vehicle control- 2mL (20mg) of sodium hyaluronate (hyaluronicacid/hyaluronan), humanserum albumin (1.2%), and PlasmaLyte A to a volume of 5mL without the human mesenchymal stem cells.	• Safety • Pain • Functional improvement • Meniscal regeneration

v. Classification of studies on the basis of level of manipulation of the stem cell/ Stem cell derived product used (*interpreted by the Secretariat as defined by CDSCO* and the information provided in the trial itself*):

S. No.	Trial Details	Intervention	Level of manipulation	Information extracted from trial
1.	Vangsness et al. 2014	human mesenchymal stem cells	More	*"The active investigational agent was a preparation of ex vivo cultured adult human mesenchymal stem cells, hMSCs (Osiris Therapeutics, Columbia, Maryland), derived from bone-marrow aspirates obtained from unrelated donors not human leukocyte antigen (HLA)-matched to recipients."*

* as defined by CDSCO in Annexure- I of the guideline document

vi. Evidence to decision framework:

QUESTION

Should Stem cell vs. standard of care be used for Meniscopathy?	
POPULATION:	Meniscopathy
INTERVENTION:	Stem cell

COMPARISON: MAIN	Standard of care
OUTCOMES:	Pain, Functional Score, Serious Adverse Events
SETTING:	Hospital/Tertiary Care setting
PERSPECTIVE:	Population
BACKGROUND:	The meniscus is composed of fibrocartilaginous tissue and plays a crucial role in providing stability, load distribution, and shock absorption within the knee joint. Injuries to the meniscus are common, and traditional treatment methods often face limitations in achieving optimal outcomes. Meniscopathy refers to any pathological condition or disorder affecting the menisci. The most common form of meniscopathy is a meniscal tear, which can occur due to traumatic injuries, degenerative changes associated with ageing, or as a result of repetitive stress on the knee joint. Meniscal tears can vary in severity, with some tears causing symptoms such as pain, swelling, and limited range of motion.
CONFLICT OF INTERESTS:	None

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○No ○Probably no ○Probably yes ●Yes ○Varies ○Don't know	The meniscus plays a vital role in maintaining the stability of the knee joint along with optimizing the tibiofemoral load transfer and distribution. This also helps in preserving the health of the articular cartilage. Meniscal tears are very common injuries of the knee for which patients seek treatment, with an estimated incidence of 61/100,000 population per year.[2] In such cases, it is vital to try and preserve the meniscus by repairing it in appropriate indications.	
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	**VAS:** Evidence from one trial, with a total of 54 participants, reporting the VAS showed a mean difference in pain reduction of 15.84 (95% CI: 6.21 to 25.46) in the stem cell transplantation arm as compared to those on usual care at the end of six months and a mean reduction of 19.55 (95% CI: 8.34 to 30.76) at the end of 12 months. There seems to be a decrease in pain, which does not cross the MCID of 20. Therefore, the reduction in pain, though statistically significant, is unimportant clinically at both time points. **Lysholm Knee Scale Score:** Evidence from one trial, with a total of 54 participants reporting the Lysholm Knee Scale score showed a mean difference of -6.66 (95% CI -20.62 to 7.30) in the stem cell transplantation arm in comparison to usual care at the end of six months and - 4.49 (95% CI -16.93 to 7.95) at the end of 12 months. The differences were statistically non-significant.	The GDG decided the MCID to be 20 %.
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ○ Moderate ○ Large ● Varies ○ Don't know	The single trial reported nine serious adverse events in eight participants which were deemed by the blinded investigators as unlikely to have been related to the investigational agent. The SAEs in the stem cell therapy included acute myocardial infarction, ileus, femur fracture, fibula fracture, osteoarthritis, meniscus lesion. The SAEs in usual care arm included small intestinal obstruction and hand fracture. The evidence is insufficient to draw firm conclusions due to limited long term follow up of the trial.	
Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

●Very low ○Low ○Moderate ○High ○No included studies	The evidence in this review is of very low quality due to single study with small sample size.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○Important uncertainty or variability ○Possibly important uncertainty or variability ●Probably no important uncertainty or variability ○No important uncertainty or variability	Main outcome is clinical improvement in the form of reduced pain and increased functional activity which is likely to be highly valued by most persons.[3, 4]	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○Favors the Comparison ○Probably favors the comparison	It is less clear if benefits of stem cell intervention outweigh the harms due to small to trivial benefit, based on limited evidence.	

● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the Intervention ○ Varies ○ Don't know		

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No direct evidence of the resources required in stem cell transplantation in patients with spinal cord injury was identified. However, indirect evidence shows that the median cost of autologous transplant was USD, $ 12,500 (range $ 10,331–39,367)-Rs. 10,00,000.	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○Very low ○Low ●Moderate ○High ○No included studies	No research evidence was identified.	The GDG members were fairly certain that stem cell therapy requires large resources.
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○Favors the comparison ●Probably favors the comparison ○Does not favor either the intervention or the comparison ○Probably favors the intervention ○Favors the intervention ○Varies ○No included studies	No research evidence was identified.	The intervention was not found to be effective and hence the committee deferred to comment on cost effectiveness.
Equity What would be the impact on health equity?		

○Reduced ●Probably reduced ○Probably no impact ○Probably increased ○Increased ○Varies ○Don't know	No research evidence was identified as stem cell therapy is an expensive treatment offered only at tertiary care centers, it is likely to increase inequity as it would not be affordable by all.	As stem cell therapy is an expensive treatment offered only at tertiary care centers, it is likely to increase inequity as it would not be affordable by all.
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○No ○Probably no ●Probably yes ○Yes ○Varies ○Don't know	Despite uncertainty regarding the medical risks and benefits associated with stem cell injections, patients with spinal cord injury have very high expectations from stem, cell therapy.[5]	
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○No ○Probably no ●Probably yes ○Yes ○Varies ○Don't know	No research evidence was identified. Stem Cell transplantation can be performed only in tertiary care centers so feasibility in lesser equipped hospitals and clinics is not possible.	Feasible to implement in tertiary centres.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Trivial	Small	Moderate	Large		**Varies**	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	**Moderate**	High			No included studies

COST EFFECTIVENESS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	**Use only in the context of rigorously conducted RCTs**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	●	○	○	○

CONCLUSIONS

Recommendation

Stem Cell Therapy is **not recommended** in routine practice for the treatment of meniscal tear/meniscopathy. It may be used only in the context of rigorously conducted randomized controlled trials.

Justification

This recommendation has been made as there is very low certainty evidence of trivial reduction in pain and no improvement in function. The undesirable effects are variable and heterogenous. In addition, the follow up period is limited to comment on long-term safety of stem cell therapy. Results should be interpreted with caution in view of various study limitations like risk of bias and small number of participants and events in the single trial.

vii. Data extraction:

Data extraction methods

A standardized data extraction form will be developed and utilized to collect relevant information from included studies. Data will be extracted on study characteristics, participant demographics, intervention details, outcomes measured, and follow-up duration.

Data extraction Sheet

Study	**Vangsness et al. 2014[1]**
Study type:	A randomized, double-blind, controlled study
Number of participants:	54
Countries and setting:	California, Florida, Illinois, Maryland, North Carolina, and Texas (United states of America)
Duration of study Follow up (post intervention):	six weeks, six months, one year, and two years postoperatively
Method of assessment of disease condition:	• Patient knee pain was assessed with use of a visual analogue scale (VAS) of 0 to 100 • Meniscal volume regeneration-MRI • Functional improvement- Lysholm knee scale
Subgroup analysis within study:	Not applicable
Inclusion criteria:	• Age 18 to 60, inclusive • In need of medial meniscectomy • Normal axial alignment • Stable knee- previous ligament reconstruction, if stable • Removal of at least 50% of the affected portion of the medial meniscus • Intact articular cartilage in posterior meniscal weight-bearing zone • Willingness to follow normal post-operative rehabilitation. • Willingness to participate in follow-up for two years from the time of meniscectomy surgery. • Ability to understand and willingness to sign consent form
Exclusion criteria:	• Pregnant or lactating • ACL or other support structure damage confirmed at surgery • Grade III or IV cartilage damage (Cartilage loss greater than 50% thickness in area >15mm on weight-bearing aspect of femoral condyle or tibial plateau) • Synvisc, steroid, or corticosteroid injections in preceding 3 months

	• Diffuse synovitis at time of arthroscopy • Inflammatory arthritis • Oral steroid, methotrexate therapy • Unable to follow post-operative exercise regimen or return for evaluations • Active alcohol or substance abuse within 6 months of study entry • Current and active tobacco product use • Patient is positive for HIV • Patient is positive for hepatitis (past history of Hepatitis A is allowed) • Any medical condition, which in the opinion of the clinical investigator, would interfere with the treatment or outcome of the patient • Indwelling pacemaker • Cerebral aneurysm clips • Ear, eye and penile implants with avian components • Electrical indwelling device such as bone stimulator • Indwelling magnets as tissue expander for future implants • Known allergy to avian, bovine or porcine protein
Recruitment/selection of patients:	Patients for a partial medialmeniscectomy based on magnetic resonance imaging (MRI) at screening andthe surgeon's evaluation meeting the50% threshold excision of the medial meniscus.
Intervention: Type of stem cells with method of their characterization, Route of administration, Dose	A single intra-articular injection of 50 or 150 million human mesenchymalstem cells suspended in 2mL (20mg) of sodium hyaluronate (hyaluronicacid/hyaluronan), human serumalbumin (1.2%), and PlasmaLyte A to a volumeof 5ml afterpartial meniscectomy.
Outcomes reported with time points:	MRI Results for Meniscal Volume, V Total Lysholm Knee Scale Scores, Knee pain was assessed with use of a 100-mmVAS six weeks, six months, oneyear, and two years postoperatively.
Funding:	Osiris Therapeutics, Columbia, Maryland (ClinicalTrials.gov: NCT00225095)
RoB2 Assessment: Specify separately for each domain	

viii. List of excluded studies:

S No.	Study	Reason of exclusion
1	Ciemniewska-Gorzela et al. 2021	Case report
2	Dancy ME et al. 2023	Non-RCT
3	Khalifeh Soltani S et al. 2019	Non-RCT
4	Mizuno M et al. 2021	Case report
5	Onoi Y et al. 2019	Case report
6	Qiao Z et al. 2020	Other disease
7	Sekiya I et al. 2022	Case report
8	Sekiya I et al. 2019	Case report
9	Sekiya I et al. 2015	Other disease
10	Koh YG et al. 2016	Other disease
11	clinicaltrials.gov/show/NCT04274543	Abstract only, Trial Incomplete/ Withdrawn
12	clinicaltrials.gov/show/NCT04972331	Abstract only, Trial Incomplete/ Withdrawn
13	Kaminski R et al. 2019	Other intervention
14	clinicaltrials.gov/show/NCT05840887	Abstract only, Trial Incomplete/ Withdrawn
15	Kalsi G et al. 2018	Other disease
16	Hershman E et al. 2021	Other intervention
17	Monllau JC et al. 2010	Other intervention
18	Izaguirre A et al. 2010	Other intervention
19	Sabater-Martos M et al. 2023	Other intervention
20	Verdonk R et al. 2010	Other intervention
21	Verdonk R et al. 2010	Other intervention
22	Verdonk PC et al. 2010	Other intervention
23	Zaffagnini S et al. 2015	Other intervention
24	Dhollander AA et al. 2017	Other intervention
25	Alley R et al. 2020	Other intervention
26	trialsearch.who.int/Trial2.aspx?TrialID=JPRN-UMIN000026383 PY- 2017	Abstract only, Trial Incomplete/ Withdrawn
27	https://trialsearch.who.int/Trial2.aspx?TrialID=JPRN-UMIN000017890 PY- 2015	Abstract only, Trial Incomplete/ Withdrawn
28	https://trialsearch.who.int/Trial2.aspx?TrialID=JPRN-UMIN000011881 PY- 2013	Abstract only, Trial Incomplete/ Withdrawn

29	https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2011-006270-13-ES PY- 2012	Abstract only, Trial Incomplete/ Withdrawn
30	Olivos-Meza A et al. 2019	Other intervention
31	Park YB et al. 2017	Case report
32	Centeno CJ et al. 2008	Other disease
33	Mahajan PV et al. 2021	Other disease
34	Katano H et al. 2021	Abstract only, Trial Incomplete/ Withdrawn
35	Cho JJet al. 2016	Other disease
36	Rue JP et al. 2008	Other intervention
37	Martinčič D et al. 2019	Other intervention
38	Benazzo F et al. 2008	Other disease
39	Takahashi T et al. 2006	Other intervention
40	Rodkey WG et al. 1999	Other intervention
41	Roemer FW et al. 2020	Other disease
42	Roemer FW et al. 2016	Other disease
43	Kaminski R et al. 2018	Other intervention
44	Kaminski R et al. 2019	Other intervention
45	Grøntvedt T et al. 1995	Other disease
46	Bouyarmane H et al. 2014	Other intervention
47	Stone KR et al. 1997	Other intervention
48	Faivre B et al. 2015	Other intervention
49	Martín-Hernández C et al. 2015	Abstract only, Trial Incomplete/ Withdrawn
50	Michael R et al. 2017	Non-RCT

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