Review of Mesenchymal Stem Cells (MSCs) and Osteoarthritis

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Osteoarthritis (OA)

- Most frequent cause of disability in US
- 10%< adult US population affected by clinical OA
- Leading indication for joint arthroplasty
- Worsening issue with aging and increasingly obese population

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Ref. [12]

Osteoarthritis in the Knee

- Pathology/findings
  - Damage/loss of articular cartilage → joint space narrowing
  - Local inflammation
  - Immunologic activity
  - Bone-spurring
- Symptoms: pain, loss of function, altered lifestyle

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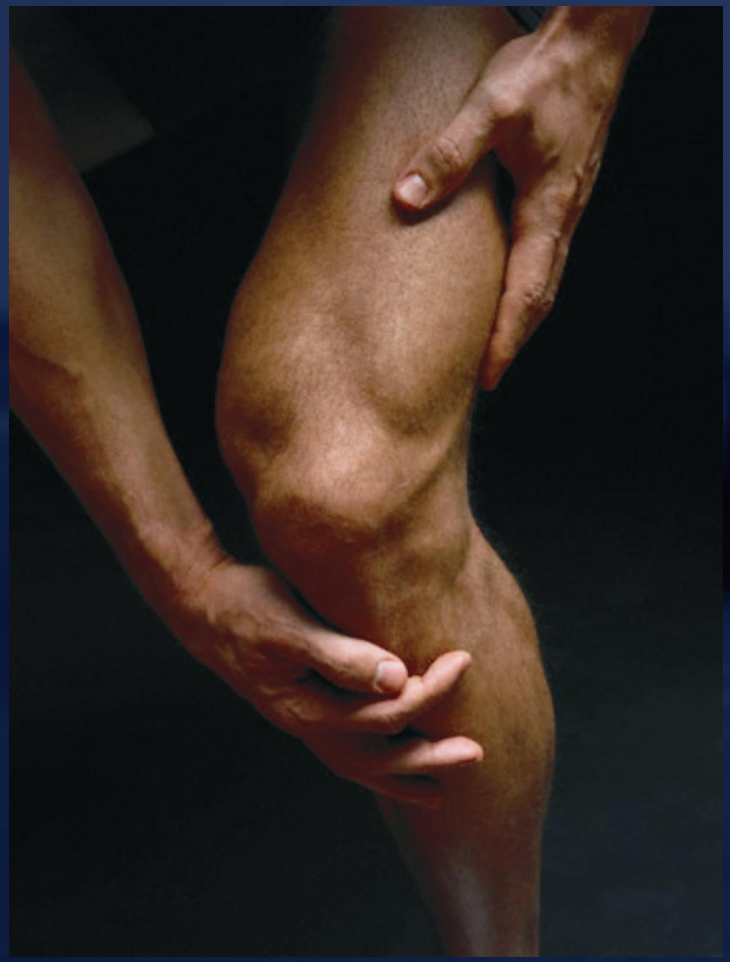
Osteoarthritis



- Risk factors
  - Age
  - Sex
  - Genetics
  - Acute injury
  - Lifestyle
  - Obesity

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Ref. [8]

Current Treatment Options

- NSAIDs
- Physical therapy
- Cortisone injections
- Hyaluronic acid injections (Synvisc, Euflexxa, Orthovisc, etc.)
- Platelet-rich plasma (PRP) injections
- Chondrocyte implantation
- Arthroscopic debridement
- Knee arthroplasty

- Current treatment options do not replace damaged cartilage or delay progression

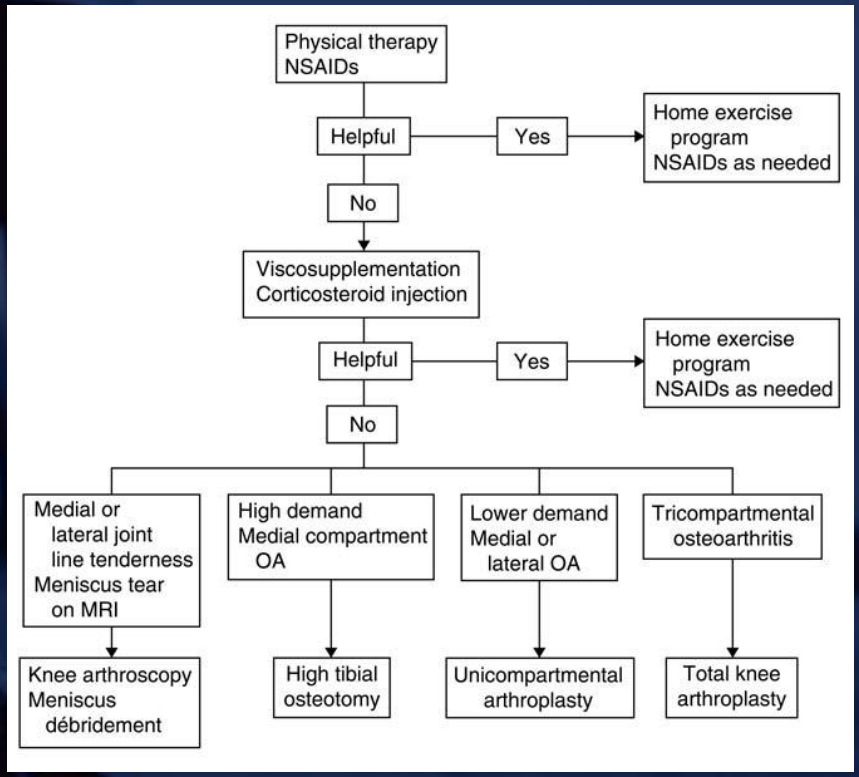

Fig 1 Treatment algorithm for knee arthritis in the young, active person.

Ref. [5]

Stem Cells and Osteoarthritis

- Dozens of animal model studies have demonstrated that mesenchymal stem cells (MSCs) can stimulate chondrogenesis in arthritic joints

- Limited clinical studies show similar results
  - Increase cartilage, relieve pain, increase function

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Ref. [2-7,10,13,14]

Mesenchymal Stem Cells (MSCs)

- Tri-potent cells that can primarily differentiate into bone (osteoblasts), cartilage (chondrocytes) or fat (adipocytes)
- Uncommitted, proliferative characteristics *in vitro*

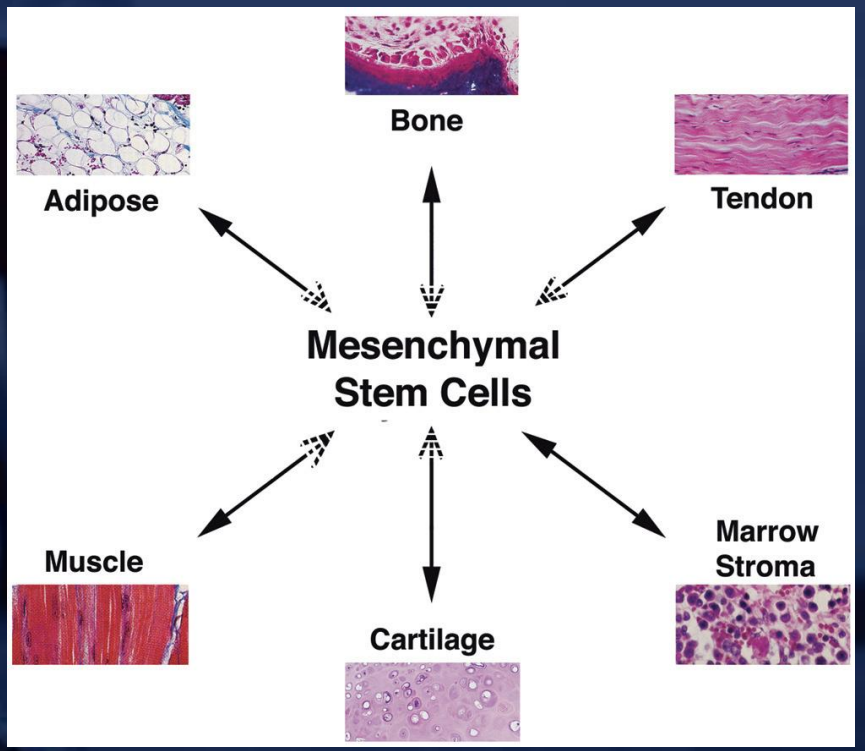
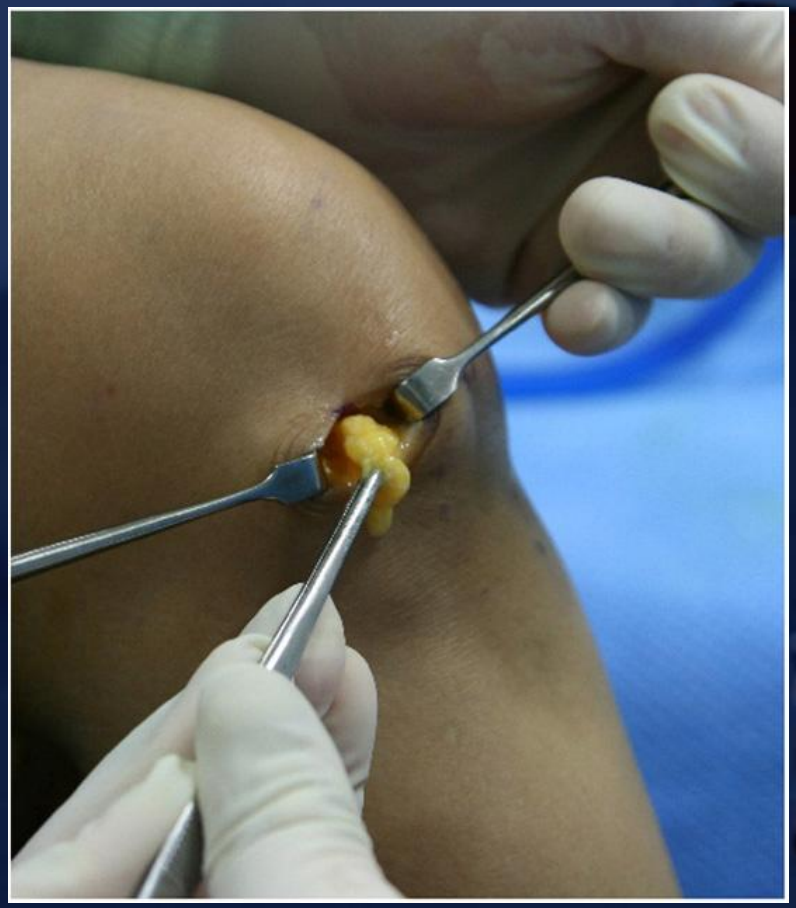


Fig 1 Multilineage differentiation potential of mesenchymal stem cells (MSCs). The arrows are presented as bidirectional, indicating that differentiated MSCs are capable of dedifferentiation and transdifferentiation.

Ref. [4]

Mesenchymal Stem Cells (MSCs)



- Isolated from:
  - Bone marrow
  - Adipose tissue
  - Periosteum
  - Synovial membrane
  - Muscle
  - Dermis
  - Articular cartilage
  - Infrapatellar fat pad

Fig. 1. Adipose synovium was harvested from the inner side of the infrapatellar fat pad by skin incision extension of the arthroscopic lateral portal site.

Ref. [6]

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Mesenchymal Stem Cells (MSCs)

- Administration
  - Scaffold
    - More invasive
    - Complex implantation procedure
    - Questionable viability of cells on scaffold and retention/degradation once implanted
  - Intra-articular injection
    - Less invasive
    - Shown to display significant benefit in human and animal studies

Ref. [3,7,10,14]

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Mesenchymal Stem Cells (MSCs)

Combat OA symptoms via:

1. Cartilage Regeneration
2. Immunosuppression
3. Anti-inflammation

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Ref. [1-4,6,7,10,13,14]

Chondrogenesis

- MSCs differentiate into chondrocytes and proliferate within damaged regions
- MSCs activate chondrogenesis in endogenous progenitor cells
  - More support in literature

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Ref. [11,13]

Murphy et al. (Arthritis Rheum 2003)

- Obtain autologous stem cells from caprine bone marrow
- Induce unilateral OA, excise medial meniscus and ACL in donor animals
- Transduce MSCs with GFP after culture
- Administer MSCs with sodium hyaluronan via intra-articular injection
- Marked regeneration of medial meniscus in treated joints
- Cartilage degeneration, sclerosis and osteophytic remodeling reduced in treated joints
- GFP visualized in small portion of medial meniscus, not in articular cartilage
- Beneficial effects of MSCs on arthritic progression may not be direct structural contribution of MSCs

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Ref. [11]

Chondrogenesis

- Many extracellular factors affect chondrogenic activity of MSCs and progenitor cells
  - Transcription factors (sox9, TGF-βs, BMPs)
  - Extracellular matrix (collagen type-II, aggrecan, cartilage oligomeric matrix protein)
- Early studies show novel cartilage produced demonstrates mechanical inferiority → more studies needed to improve environmental conditions

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Ref. [4]

Immunosuppresion

- Inhibit T-cell activation and proliferation
  - Dosage-dependent
- Inhibit proliferation of B-cells, natural killer (NK) cells and dendritic cells
  - Inhibit B-cell antibody production
  - Inhibit NK cytotoxicity

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Ref. [4]

Immunosuppression Mechanism

- Evidence indicates MSCs alter dendritic, T and NK cell cytokine secretion
  - Reduce pro-inflammtory cytokine secretion (TNF-α, IFN-γ)
  - Upregulate anti-inflammatory cytokines (IL-4, IL-10)

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Ref. [1,4]

Anti-inflammation

- Anti-inflammatory effect believed to result from immunoregulation
- MSCs can be administered with PRP or HA for additional anti-inflammatory effect
- MSCs and differentiated progeny illicit anti-inflammatory effect

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Ref. [4]

Case Studies

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Centeno *et al.* (*Pain Physician* 2008)

- N=1, case study
- MSCs harvested from bone marrow of the iliac crest, cultured for growth
- 22.4M MSCs in PBS administered via intra-articular injection with nucleated cells suspended in PBS (repeat at 1 and 2 weeks, 2 week injection with 1 ml of 10ng/ml dexamethasone)
- VAS and ROM significantly improved over 3 mos
- Cartilage surface volume and meniscal volume significantly increased as seen on MRI

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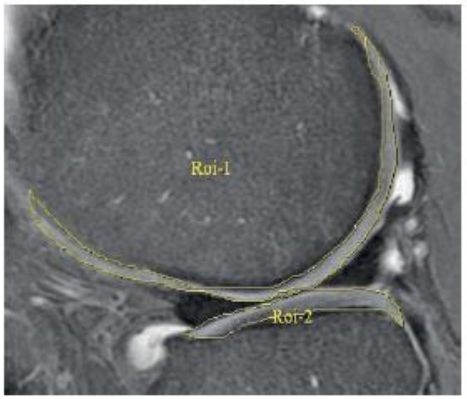
Ref. [3]

Centeno *et al.* (*Pain Physician* 2008)

Increased Knee Cartilage Volume Using Autologous Mesenchymal Stem Cells



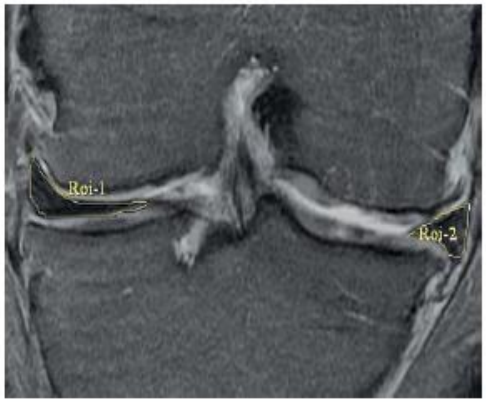
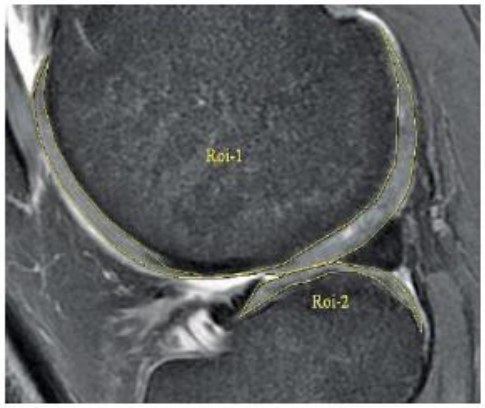


Fig.1. Pre-injection. Left shows cartilatge and right shows meniscus.



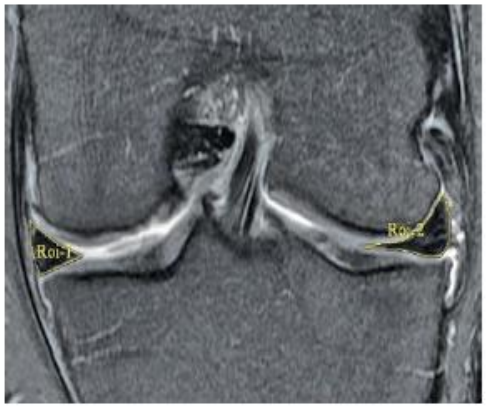


Fig.2. Six months post-injection. Left shows cartilatge and right shows meniscus.

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Ref. [3]

Koh *et al.* (*Arthroscopy* 2013)

- N=18 (6 men, 12 women)
- MSCs obtained from infrapatellar fat pad
- MSCs (mean =$1.18x10^6$) injected with 3mL PRP after arthroscopy, 1 week and 2 weeks s/p surgery
- Pain scores and Lysholm scores decreased significantly at final follow-up (24-26 mos)
- Whole-organ MRI scores improved significantly, esp. cartilage whole-organ MRI score

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Ref. [7]

Koh *et al.* (*Arthroscopy* 2013)

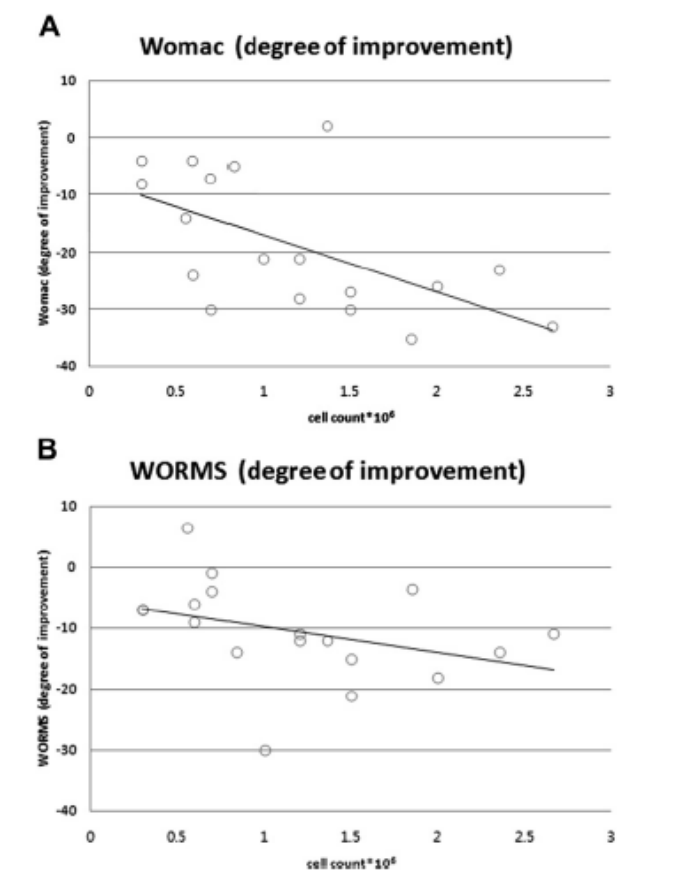

Fig 2. Correlations between patient outcomes and number of stem cells injected. (A) The negative correlation between WOMAC score and number of cells injected indicates that treatment with larger quantities of stem cells results in improved outcomes. (B) The negative correlation between the WORMS cartilage subscore and the number of stem cells injected suggests that improved outcomes are the result of treatment with larger quantities of stem cells.

Benefits correlated to the number of MSCs injected

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Ref. [7]

Koh *et al.* (*Arthroscopy* 2013)

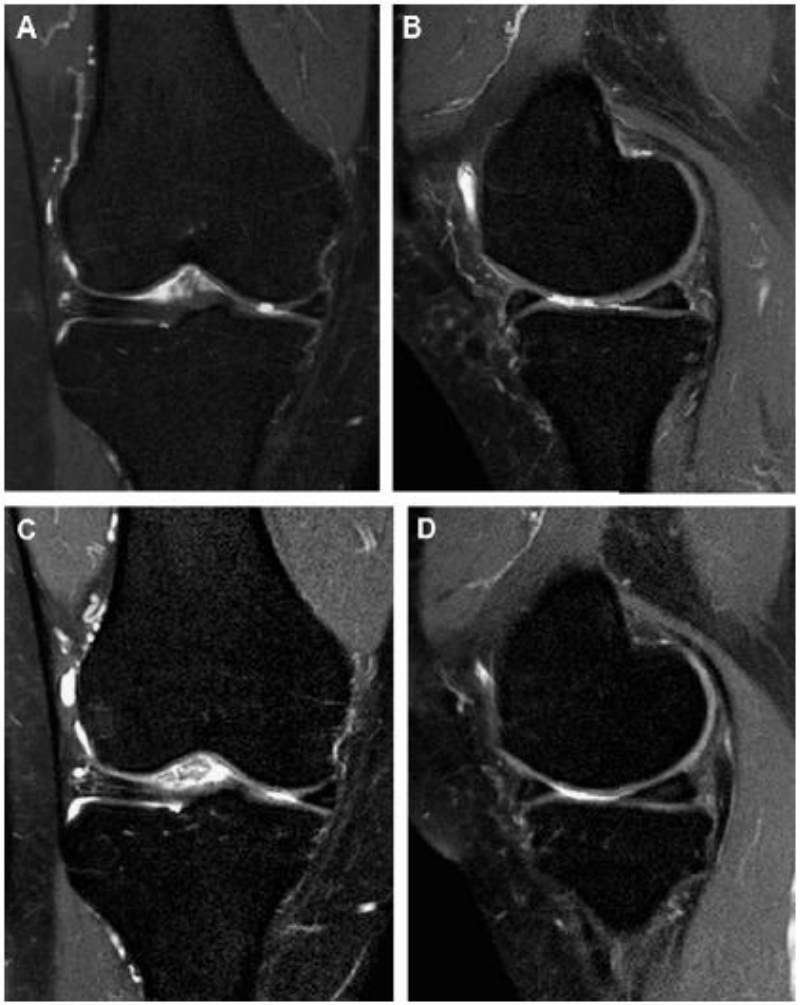

Fig 3. Results of MRI performed preoperatively (A and B) and postoperatively (C and D) on a 45-year-old female patient. This MRI is not representative of all MRIs observed in the study but is explored in further detail because the effects of the treatment were particularly dramatic in this patient. (A) Fat-saturated proton-density fast spin-echo coronal view and (B) T1-weighted fast spin-echo sagittal view of osteochondral defects of medial femoral condyle. (C) Fat-saturated proton-density fast spin-echo coronal view and (D) gradient-echo sagittal view of same patient at 2-year follow-up visit.

Ref. [7]

Lee *et al. (Arthroscopy* 2013)

- Stem cell/PRP injections effectlively shown to repair osteochondral deffects in an animal model
- PRP prepared from rabbit blood
- MSCs obtained from infrapatellar fat pad
- Three treatment groups
  - Untreated
  - PRP injection only
  - PRP and MSCs ($2x10^7$ cells/mL) injected

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Ref. [9]

Lee *et al. (Arthroscopy* 2013)

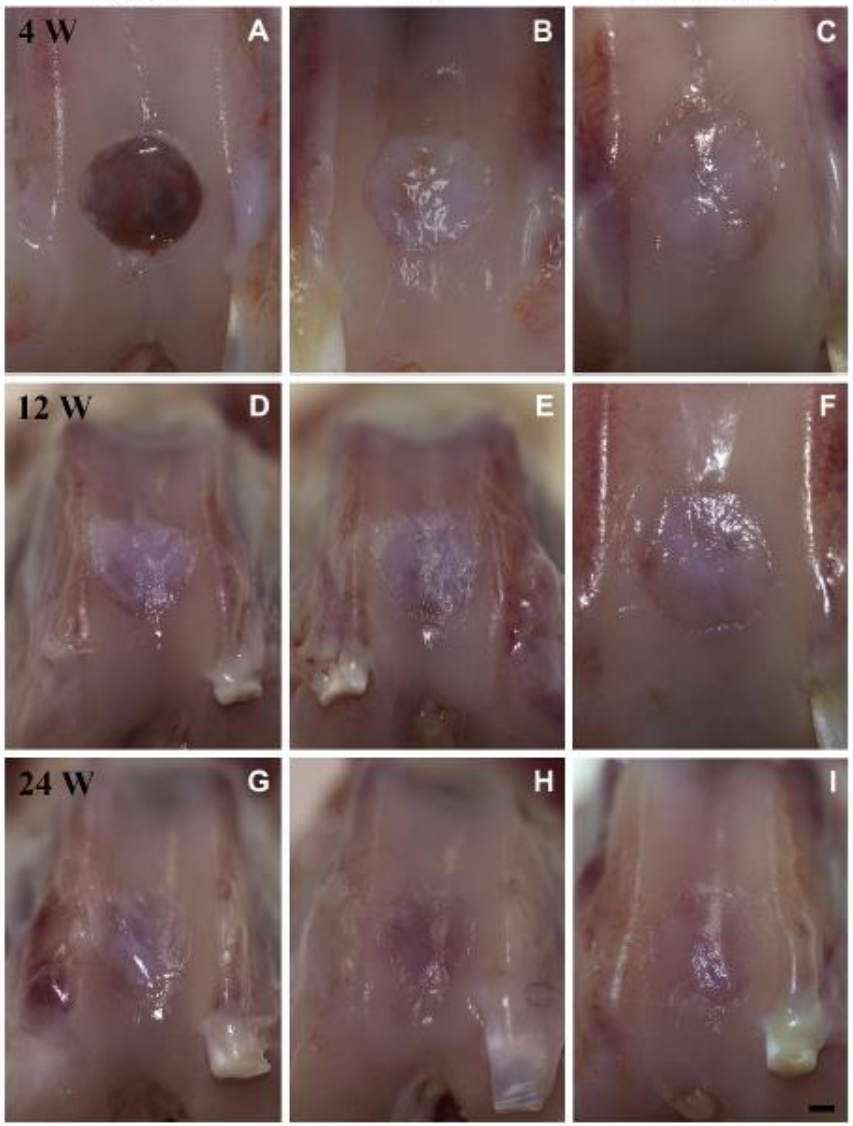

Fig 3. Macroscopic appearance of (A-C) defects in trochlear groove (4 mm in diameter) at 4 weeks (4 W), (D-F) 12 weeks (12 W), and (G-I) 24 weeks (24 W) after surgery in (A, D, G) control group, in which transplantation was not performed; (B, E, H) PRP group; and (C, F, I) PRP-SDSC group (scale bar, .7 mm).

Ref. [9]

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Lee *et al. (Arthroscopy* 2013)

- In the control group, the defect was repaired by fibrous tissue
- In both treatment groups, the defect was repaired with hyaline cartilage
  - PRP only – irregular cell structure and junction with subchondral bone
  - PRP + MSCs – well aligned chondrocytes, well remodeled subchondral bone; histological analysis showed superior tissue compared with PRP injection alone

Ref. [9]

References

1. Aggarwal S, Pittenger MF. Human mesenchymal stem cells modulate allogeneic immune cell responses. *Blood* 2005;105:1815-1822.
2. Ahmad Z, Wardale J, Brooks R, Henson F, Noorani A, Rushton N. Exploring the application of stem cells in tendon repair and regeneration. *Arthroscopy* 2012;28:1018-1029.
3. Centeno CJ, Busse D, Kisiday J, Keohan C, Freeman M, Karli D. Increased knee cartilage volume in degenerative joint disease using percutaneously implanted, autologous mesenchymal stem cells. *Pain Physician* 2008;11:343-353.
4. Chen FH, Tuan RS. Mesenchymal stem cells in arthritic diseases. *Arthritis Res Ther* 2008;10:223.
5. Feeley BT, Gallo RA, Sherman S, Williams RJ. Management of osteoarthritis of the knee in the active patient. *J Am Acad Orthop Surg* 2010;18:406-416.
6. Koh YG, Choi YJ. Infrapatellar fat pad-derived mesenchymal stem cell therapy for knee osteoarthritis. *Knee* 2012;19:902-907.
7. Koh YG, Jo SB, Kwon OR, et al. Mesenchymal stem cell injections improve symptoms of knee osteoarthritis. *Arthroscopy* 2013;29:748-755.
8. Koonce RC, Bravman JT. Obesity and osteoarthritis: more than just wear and tear. *J Am Acad Orthop Surg* 2013;21:161-169.
9. Lee JC, Min HJ, Park HJ, et al. Synovial Membrane-Derived Mesenchymal Stem Cells Supported by Platelet-Rich Plasma Can Repair Osteochondral Defects in a Rabbit Model. *Arthroscopy* 2013;29:1034-1046.
10. Lee KB, Hui JH, Song IC, Ardany L, Lee EH. Injectable mesenchymal stem cell therapy for large cartilage defects--a porcine model. *Stem Cells* 2007;25:2964-2971.
11. Murphy JM, Fink DJ, Hunziker EB, Barry FP. Stem cell therapy in a caprine model of osteoarthritis. *Arthritis Rheum* 2003;48:3464-3474.
12. Murphy L, Helmick CG. The impact of osteoarthritis in the United States: a population-health perspective: A population-based review of the fourth most common cause of hospitalization in U.S. adults. *Orthop Nurs* 2012;31:85-91.
13. Pak J. Regeneration of human bones in hip osteonecrosis and human cartilage in knee osteoarthritis with autologous adipose-tissue-derived stem cells: a case series. *J Med Case Rep* 2011;5:296.
14. Sato M, Uchida K, Nakajima H, et al. Direct transplantation of mesenchymal stem cells into the knee joints of Hartley strain guinea pigs with spontaneous osteoarthritis. *Arthritis Res Ther* 2012;14:R31.

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