Conservative options-OA, Orthobiologics

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Conservative treatment options

- Physiotherapy
- orthobiologics

Orthobiologics

- Defined by the American Academy of Orthopaedic Surgeons (AAOS) are **biological substances found naturally in the body that help injuries heal more quickly**.
- Biologically derived conductive material that aids in repair and regeneration of bone, muscle, tendons, ligaments and cartilage.

Orthobiologics

- Platelet-rich plasma (PRP)
- Prolotherapy
- Ozone therapy
- Autologous conditioned serum (ACS)
- Bone marrow aspirate concentrates (BMACs),
- Adipocyte-derived stem cells
- Mesenchymal-derived concentrates
- Amniotic-derived cell concentrates
- Cord blood–derived cell concentrates
- Interleukin therapies
- Alpha-2 macrophages.

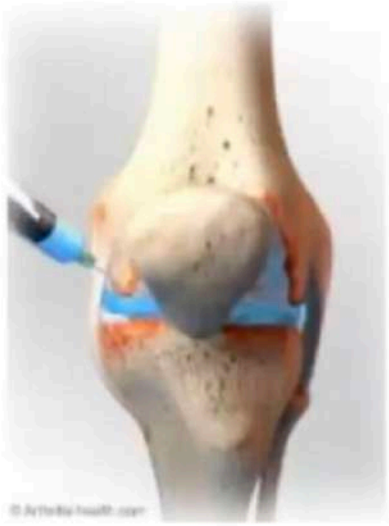
In focus – Clinical use

- Viscosupplementation
- PRP
- ACS (Autologous conditioned serums)
- BMACs (Bone marrow aspirate concentrates)
- Cell-derived therapies

IA Corticosteroids

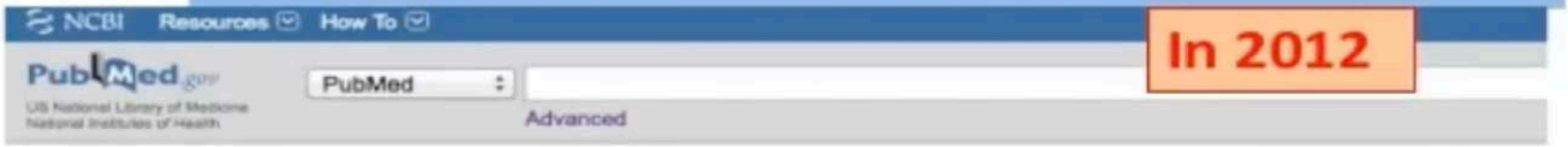
Preffered as the last non operative modality

- Initial injections were steroids, with multi purpose use: *Pain relief, Anti inflammatory, Instinct?*



Raynauld JP et al. Safety and efficacy of long term intraarticular steroid injections in OA knee: a randomized, double blind, placebo controlled trial. Arthritis Rheum 2003;48(2):370-377.

What are the recommendations?



In 2012

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Pain Med. 2012 Jun;13(6):740-53. doi: 10.1111/j.1526-4637.2012.01394.x. Epub 2012 May 23.

Evidence-based knee injections for the management of arthritis.

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Abstract

OBJECTIVE: Arthritis of the knee affects 46 million Americans. We aimed to determine the level of evidence of intraarticular knee injections in the management of arthritic knee pain.

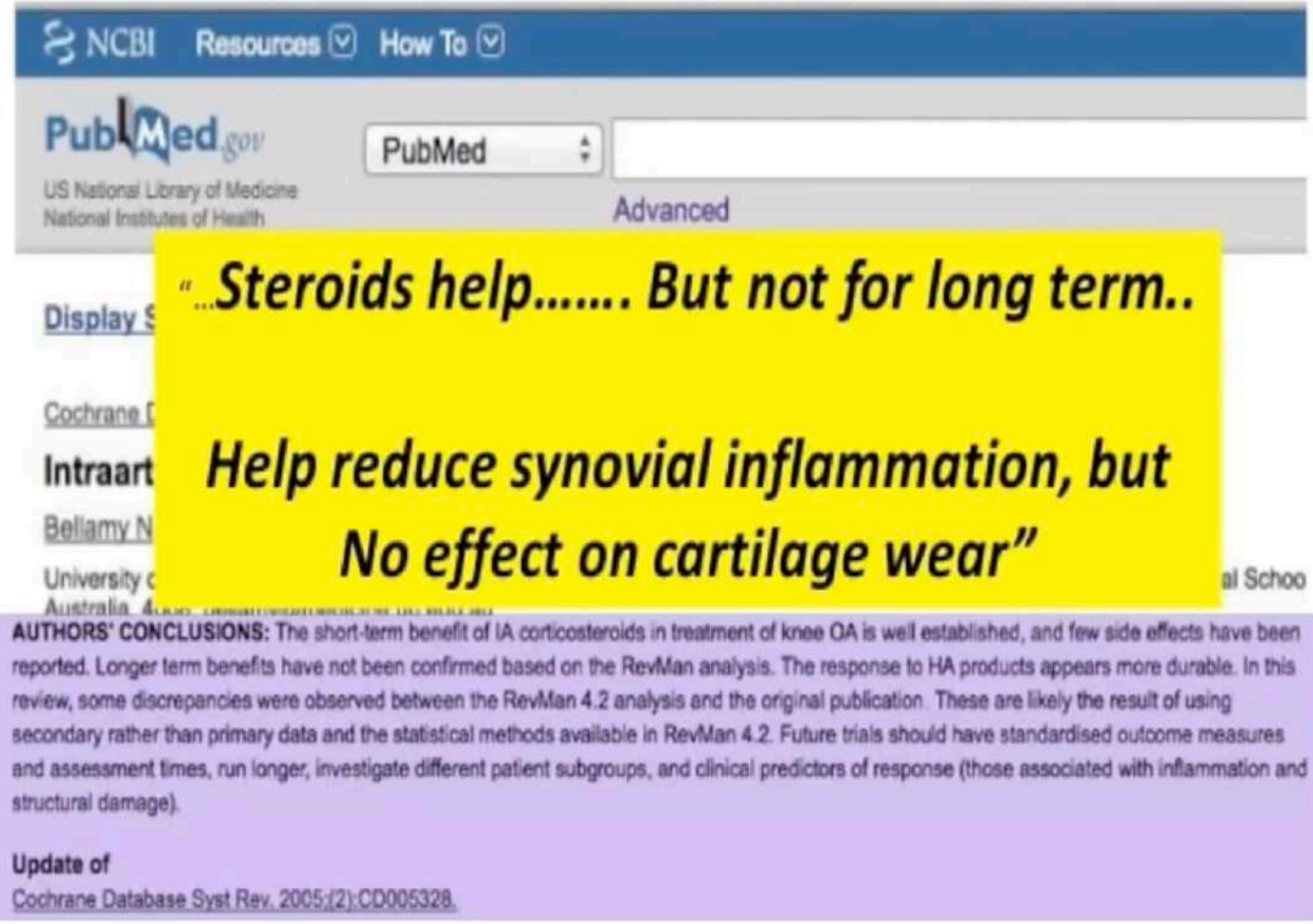
METHODS: We systematically searched PUBMED/MEDLINE and the Cochrane databases for articles published on knee injections and evaluated their level of evidence and recommendations according to established criteria.

Strong evidence supports the use of intra-articular Injections as a valuable intervention in the continuum of management of arthritis……..”

provided various degrees of success, but their long-term safety and efficacy remains to be determined.

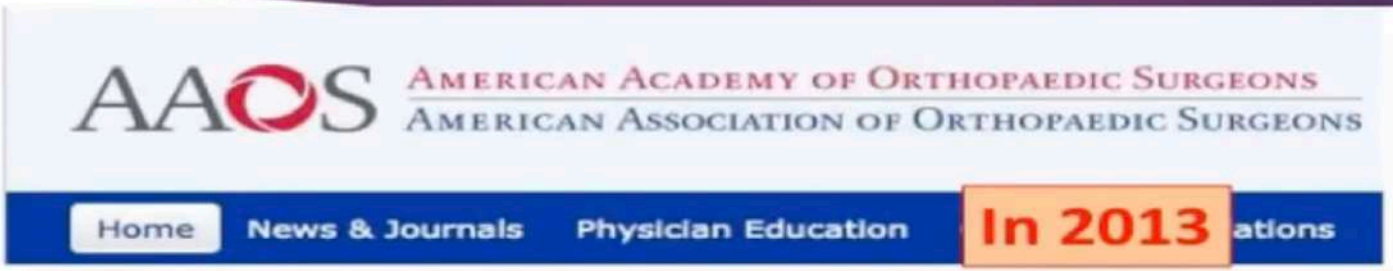
CONCLUSIONS: We conclude that strong evidence supports the use of intraarticular knee injection as a valuable intervention in the continuum of management of arthritis between conservative treatment and knee surgeries.

BUT: Which type of injections?



"...Steroids help..... But not for long term..

Help reduce synovial inflammation, but No effect on cartilage wear"



Procedural Treatments: Recommendation 8-11

RECOMMENDATION 8

We are unable to recommend for or against the use of intraarticular (IA) corticosteroids for patients with symptomatic osteoarthritis of the knee.

Strength of Recommendation: Inconclusive

Jones A, Doherty M. Intra-articular corticosteroids are effective in osteoarthritis but there are no clinical predictors of response. Ann Rheum Dis 1996;55(11):829-832

Consensus

- Adjunct to core treatments!
- Relieves moderate to severe pain in some cases
- Joint effusion aspiration with injection in Grades 2/3 OA gives short term relief
- Does NOT degrade cartilage further

National Collaborating Centre for Chronic Conditions (UK). Osteoarthritis: National clinical guideline for care a&management in adults. London: Royal College of Physicians (UK), 2008

VISCOSUPPLEMENTATION

- hyaluronic acid (HA) treatments injected into the joint for pain relief and possible anti-inflammatory effect
- **HA - anionic, non-sulfated glycosaminoglycan (**found in connective tissues, epithelium, and neural tissue)
- formed in the plasma membrane
- main components of the extracel- lular matrix, contributing to cell proliferation and migration
- providing viscoelastic properties to the synovial fluid.

HA

- **Healthy adult knee** with no pathology - concentration of HA is between **2.5 and 4.0 mg/mL**
- **Arthritic knee** – decreases by 33% to 50%

  - size of the HA molecules is reduced

  - less inter-molecular interaction

  - ultimately leading to decreased dynamic viscosity and elastic properties

Vissco Supplements

- Designed as Synovial fluid Prosthetic device to lubricate the joint
- Different Molecular wts, provide different levels of lubrication

Maneiro E, et al. The biological action of hyaluronan on human osteoarthritic articular chondrocytes: the importance of molecular weight. Clin Exp Rheumatol 2004; 22: 307-312

Mechanism of action

- **Viscoinduction-** production of HA from chondrocytes and synoviocytes
- **Chondroprotection -** preventing cartilage fragmentation
- **Viscosupplementation -** provide protection from mechanical stress

interaction of HA with the cluster of differentiation 44 (CD44) receptors. → inhibitory effect on interleukin-1ß → decreases the production of matrix metalloproteinase → downregulates the catabolic effect on cartilage.

Common Brands of High Molecular Weight Hyaluronic Acid and Their Characteristics

Brand	No. of Injections	Injection Amount, mL	Source
Euflexxa[8]	3	2	Bacteria
Synvisc[9]	3	2.25	Avian
Synvisc-One[10]	1	6	Avian
Supartz[11]	3 or 5	2.5	Avian
Durolane[12]	1	3	Bacteria
Hyalgan[13]	3 or 5	2	Avian
Orthovisc[14]	3 or 4	2	Bacteria

Adverse effects

- No serious adverse effects
- Common non serious – arthralgia, joint swelling
- The rates of adverse reactions varied from 0% to 14.4%
- Repeat injections did not have increased rates of adverse effects compared with single injections

Role in OA

- **Controversial**
- **In 2013, the American Academy of Orthopaedic Surgeons** released its clinical practice guidelines for osteoarthritis, stating that the use of **HA in osteoarthritis** is **not supported**
- In **2015, a systematic review by Campbell et al** indicated that when compared with nonsteroidal anti- inflammatory drugs, corticosteroid, PRP, and placebo, HA had the highest level of evidence supporting its use for early osteoarthritis, showing improvements in function and pain for up to 26 weeks.
- **Consensus :** moderate osteoarthritis (Kellgren–Lawrence grade II–III)

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RECOMMENDATION 9

We cannot recommend using hyaluronic acid for patients with symptomatic osteoarthritis
knee.

Strength of Recommendation: Strong

AAOS has changed its guideline given in 2008 where it had medium evidence in support

Clinical scenarios for the use of HA listed by Bhadra and colleagues	
1. Symptomatic adults with mild or moderate OA of the knee who have clinically and radiologically confirmed disease who have not received other therapies for the knee	Appropriate
2. Symptomatic adults with severe mild or moderate OA of the knee who have clinically and radiologically confirmed disease and have failed other nonpharmacologic or pharmacologic therapies for the knee	Appropriate
3. Symptomatic adults with mild or moderate OA of the knee who have clinically and radiologically confirmed disease who have incomplete response to other therapies for the knee	Appropriate
4. Symptomatic adults with mild or moderate OA of the knee who are intolerant of, have a high-risk of adverse reaction to, or who are contraindicated for pharmacologic agents for the knee (oral, topical, or intra-articular)	Unclear
5. Symptomatic adults who have mechanical meniscus pathology with underlying OA of the knee	Unclear
6. Symptomatic adults with OA of the knee who have had a significant adverse reaction to an intra-articular HA product	Unclear
7. Symptomatic adults with OA of the knee who have active inflammatory arthritis (rheumatoid arthritis, gout, and so forth)	Unclear
8. Symptomatic adults with OA of the knee who have synovitis of the knee with significant effusion	Unclear

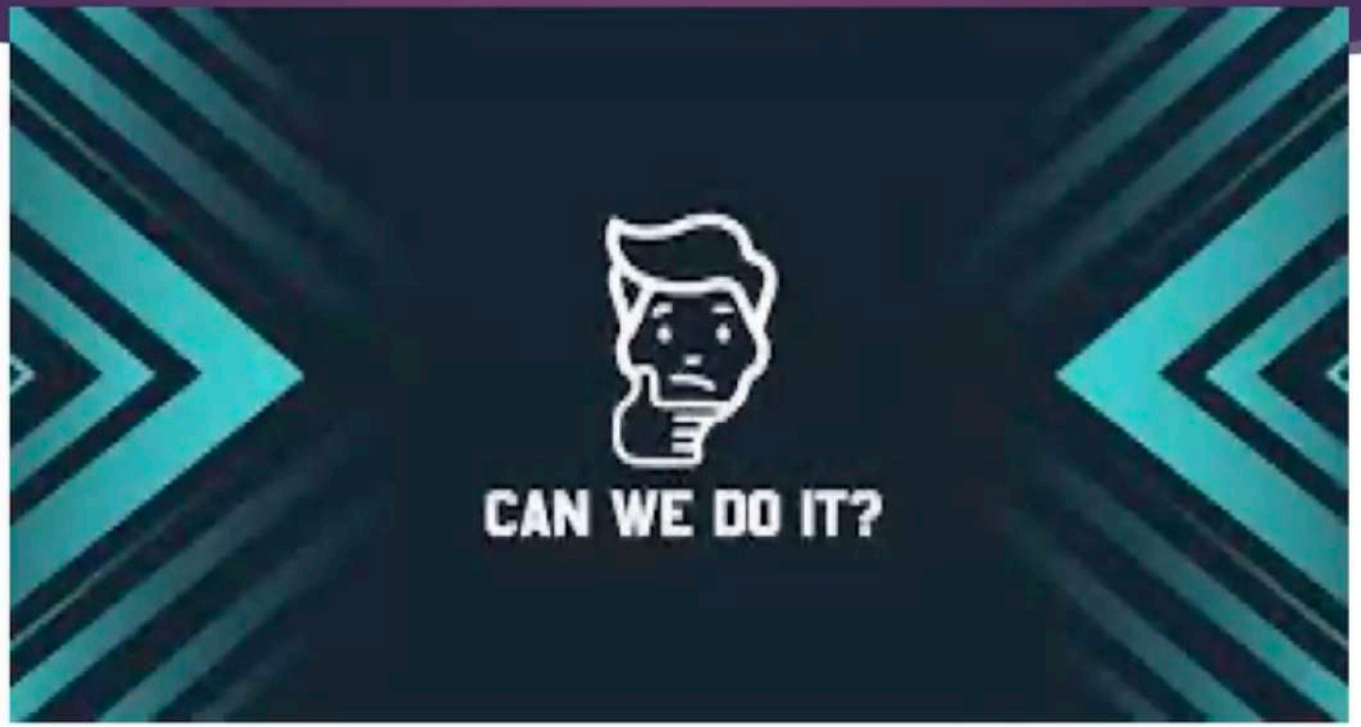
From Bhadra AK, Altman R, Dasa V, et al. Appropriate use criteria for hyaluronic acid in the treatment of knee osteoarthritis in the United States. Cartilage 2017;8(3):234–54; with permission.

Consensus

- Research evidence suggests that IA HA injections are safe, have potential efficacy,
- Provide pain reduction in EARLY OA for upto 24 weeks
- COST effectiveness is a concern.
- Patient must be aware of the limitations

Rutjes AW,et al. Viscosupplementation for osteoarthritis of the knee: a systematic review and meta-analysis. Ann Intern Med 2012; 157: 180-191

Cartilage Regeneration



PRP – platelet rich plasma

- Use rapidly expanded over the last decade

Mechanism of Action

Platelet-rich plasma contains supra-physiologic concentrations of platelets → release cytokines and growth fac- tors that are involved in the facilitation of tissue healing and regeneration.

↓

strong chemotactic effect on chondrocytes and mesenchymal stem cells → mitogenic benefit resulting in the increased production of proteoglycans and heterotopic cartilage

PRP works to modify gene expression

↓

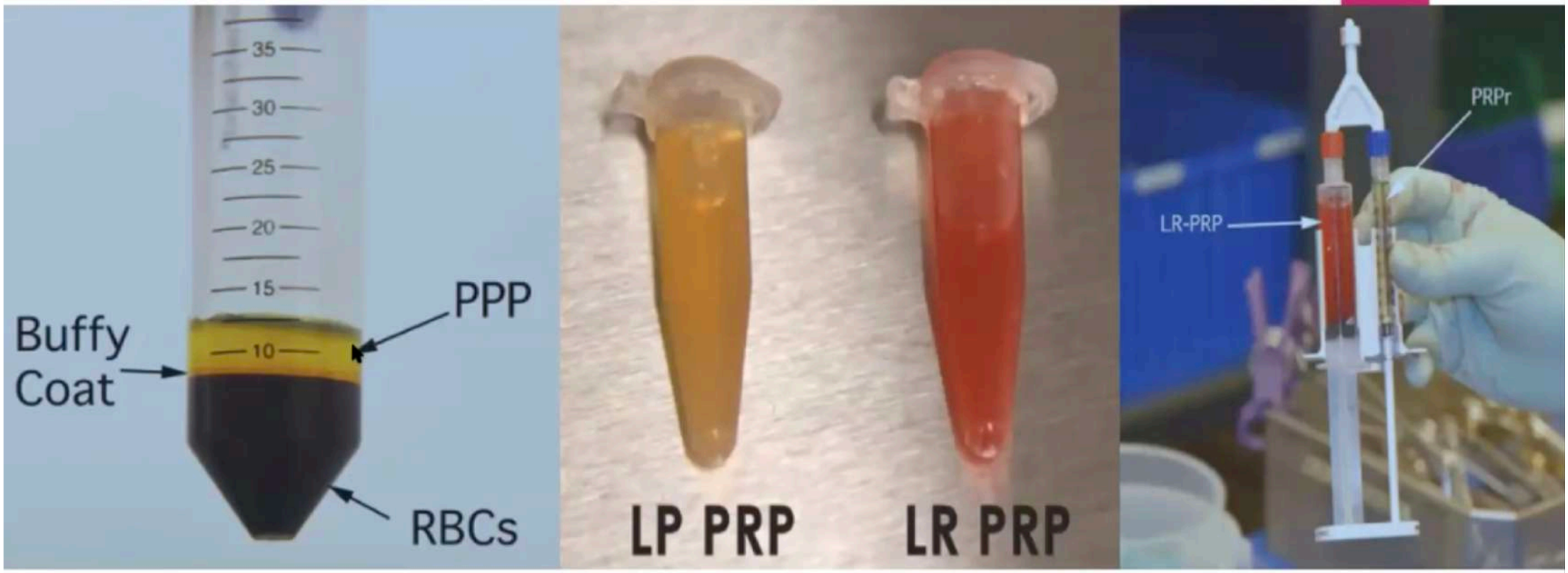
inhibit the production of matrix metalloproteinase 13 and nuclear factor-kappa B

↓

Decreases the inflammatory environment known to characterize the pathogenesis of osteoarthritis.

Types and Processing

- Platelet-rich plasma is produced by drawing a patient's blood via standard venipuncture
- centrifuge to separate the components into layers **(differential centrifugation).**
- whole blood is separated into 3 layers. The **red blood cells** settle to the **bottom**, **platelets and some white blood cells** form the **upper layer**, and the **middle layer or "buffy coat" is rich in white blood cells.**
- **Platelet concentrates** have been recorded as between **200 * 10^3 and 1000 *10^3 platelets per microliter,** with no consensus existing as to which concentration has the best outcomes.



Role in OA

- Controversial
- Preclinical studies have been supportive of the use of PRP for the regeneration of joint tissue in OA.
- LP-PRP provided better functional outcomes compared with placebo versus LR-PRP
- increased adverse events compared with HA or placebo

Summary of meta-analyses looking at PRP

Study	Studies Included	Databases	Dates	Comparison	Sample Size	Average Follow- up	Outcome Measures	Results
Chang et al,[40] 2014	16 Studies • 8 single arm • 3 quasi-experimental • 5 RCTs	MEDLINE	2010–2013	PRP vs HA	1543	12 mo	IKDC KOOS WOMAC	PRP significantly improved scores more than HA. PRP was more effective in less severe OA.
Laudy et al, 2014	10 Studies • 6 RCTs • 6 non-RCTs	MEDLINE Embase CINHAL Web of Science Cochrane database	2011–2013	PRP vs HA PRP vs placebo	1110	6 mo	WOMAC VAS NRW Lequesne	PRP significantly improved scores than HA. PRP significantly improved scores more than placebo.
Riboh et al, 2015	9 Studies • 6 RCTs • 3 prospective	MEDLINE Embase Cochrane database	2011–2013	LP PRP vs LR PRP	1055	Not reported	IKDC WOMAC Adverse reactions VAS Lequesne Tegner Marx KOOS SF-36 MRI	LP-PRP improved WOMAC scores compared with placebo. There were similar adverse events between LP-PRP and LR-PRP.

Meheux et al,[43] 2016	6 Studies	PubMed Cochrane database Central register of controlled trials Scopus Sport discus	2011–2015	PRP vs HA	739	6–12 mo	WOMAC IKDC KOOS VAS Lequesne	PRP had improved outcomes compared with baseline greater than HA.
Sadabad et al,[44] 2016	6 Studies	PubMed Cochrane database Scopus Void database	2005–2015	PRP vs HA	722	5–48 wk	WOMAC	PRP significantly improved WOMAC scores than HA.
Dai et al,[45] 2017	10 RCTs	PubMed Embase Scopus Cochrane database	2011–2016	PRP vs HA PRP vs saline	1069	3–12 mo	WOMAC IKDC Lequesne	At 6 mo, there was no difference between treatments. At 12 mo, PRP had improved outcomes compared with both HA and saline.

Abbreviations: CINHAL, Cumulative Index to Nursing and Allied Health Literature; IDKC, International Knee Documentation Committee; KOOS, Knee Injury and OA Outcome Score; SF-36, 36-Item Short-Form Health Survey.

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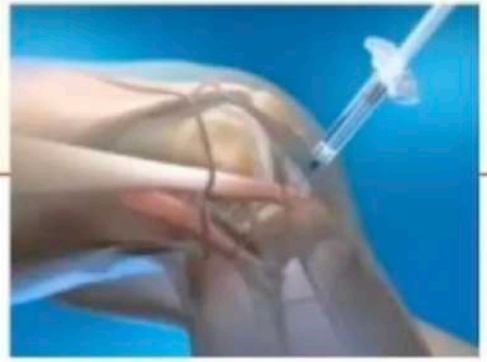
RECOMMENDATION 10

We are unable to recommend for or against growth factor injections and/or platelet rich plasma for patients with symptomatic osteoarthritis of the knee.

Strength of Recommendation: Inconclusive



Bone Marrow Aspirate Concentrate

- most commonly harvested from the **iliac crest, distal femur, proximal tibia, proximal humerus, and calcaneus.**
- Most common stem cell based therapy used in OA
- Iliac crest – best source

Table 2

Commonly Used Systems to Concentrate Bone Marrow Aspirate and Their Characteristics

System	Input Volume, mL	BMAC Output, mL	Centrifuge Time, min	Centrifuge Speed, rpm
Angel[53]	40-180	Adjustable	15-26	3200
BioCUE[54]	30 or 60	3 or 6	15	3200
Arteriocyte Magellan[55]	30-60	3-10	12-17	2800 and 3800
ART BMC[56]	60	3.5-4	15	Not mentioned
Exactech[57]	60	6	10 or 12	2400 or 3600

Abbreviation: BMAC, bone marrow aspirate concentrate.

Role in OA

- Still under investigation
- many studies showing good to excellent degrees of improvement in pain and function with minimal adverse reactions
- No randomized trials
- **Kim et al and Shapiro et al** comparing BMAC with saline injections for patients with bilateral knee osteoarthritis did not show a statistically significant difference in patient outcomes through 12 months.

AdiPose-derived mesenchymal stem cells

- Minimally manipulated cell therapy
- abundance of progenitor cells, with high concentrations of nucleated cells extracted per harvest.
- harvested via a lipoaspirate technique using subcutaneous fat (**abdomen, flank, or buttocks**) or **arthroscopically from the infrapatellar fat pad.**
- isolating the adipose-derived mesenchymal stem cells from the adipocytes and extracellular tissues
- the ultimate goal is to isolate the **stromal vascular fraction**, which is thought to contain the majority of the progenitor cells

Techniques for processing

- **Micro-fragmentation and cleansing**
- **vibrational energy**
- **Enzymatic digestion**
- **Differential centrifugation** to form the ultimate product
- **Not currently approved by the US Food and Drug Administration**

Role in OA

- no randomized, placebo- controlled clinical trials exist evaluating the use of stromal vascular fraction or adipose-derived mesenchymal stem cells in osteoarthritis.
- Phase I clinical trials have shown the safety of adipose-derived mesenchymal stem cells, with only minor local adverse effects.

Tissue Engineering

- Tissue engineering combines cells with a three- dimensional (3D) biomaterial scaffold to help regenerate damaged tissue.
- 3D microenvironment that resembles specific tissues and stimulate native tissue regeneration by promoting cell-matrix and cell-cell interactions, which can lead to cell dif- ferentiation and tissue growth
- **Synthetic Biodegradable Scaffolds - 3D poly- lactic-co-glycolic acid (PLGA)** scaffold to provide architectural support for MSC differen- tiation and chondrogenesis for cartilage repair without using any growth factors.
- **Composite (Natural-Synthetic) Scaffolds**
- **Natural Biodegradable Scaffolds**

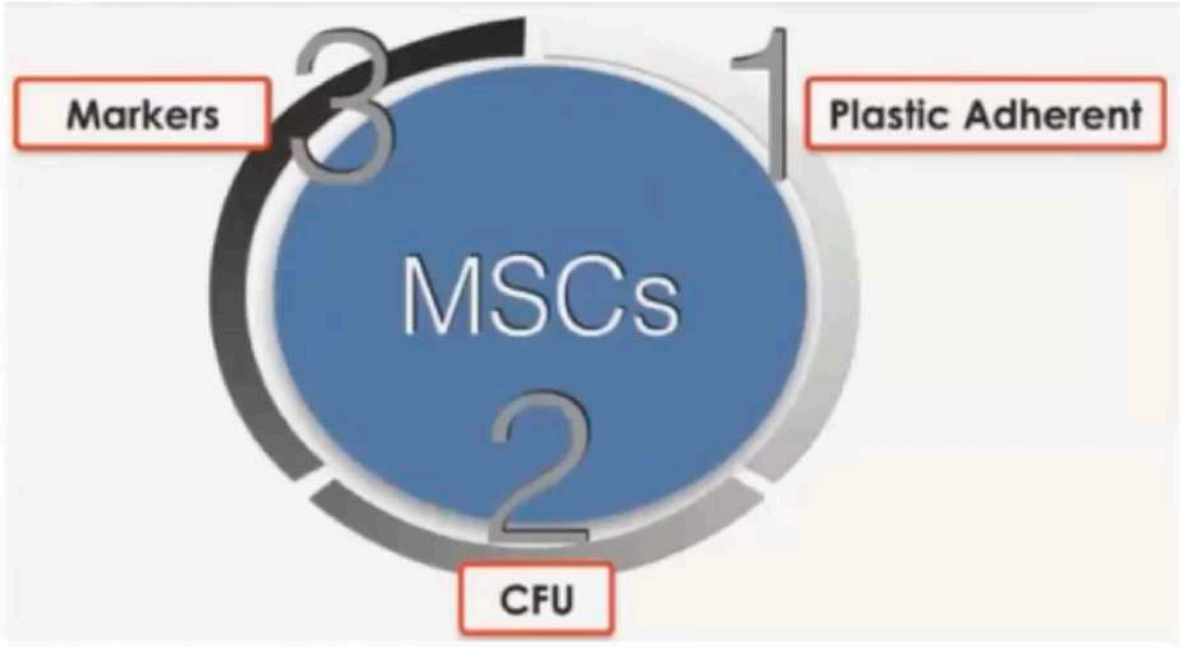


Fig. 11.6 Diagram demonstrating the minimal criteria for a human progenitor cell to be classified as a mesenchymal stem cell (MSC). (1) It must adhere to plastic when maintained in standard culture conditions. (2) It must be able to differentiate and proliferate in colonies (CFU, colony forming unit) of osteoblasts, adipocytes, and chondroblasts in vitro. (3) It must demonstrate a particular expression and lack of expression of cell markers

Conclusion : role of biologics

- Lack of high-level evidence
- Role of biologics in the treatment of both osteoarthritis remains controversial
- Good safety profile without significant adverse effects