

## Is it the time of a paradigm shift from intra-articular corticosteroid injections to regenerative medicine in osteoarthritis? review article

Hassan Mubark\*

Rheumatologist, Auckland Regenerative Clinic, Ormiston Specialist Centre, 125 Ormiston Road, Flat Bush, Auckland 2019, New Zealand.

### \*Corresponding author

Hassan Mubark, Rheumatologist, Auckland Regenerative Clinic, Ormiston Specialist Centre, 125 Ormiston Road, Flat Bush, Auckland 2019, New Zealand.

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### Abstract

This article addresses the best practice in managing osteoarthritis (OA), weighing the benefits and risks of various intra-articular therapies.

For many decades we had used intra-articular injections of corticosteroids (IACSs) as the only option after analgesics and physical therapy to help symptoms in patients who suffer from mild to moderate OA until they get ready for joint replacement. In advanced degenerative diseases, particularly in the elderly, we go directly to surgery except when there are multiple comorbidities, then surgery is not an option; thus, IACS injection is the only option left. Furthermore, in individuals suffering from renal disease, peptic ulcer, diabetes, or heart failure, we cannot use regular non-steroidal anti-inflammatory medicines, going the only option for frequent IACSs.

Several kinds of literature suggest some harmful effects of IACSs. These include accelerated OA of the cartilage, subchondral insufficiency fracture, joint infection, and osteonecrosis.

As the science progresses, regenerative therapies (RTs) emerge, including hyaluronic acid (HA), platelet-rich plasma (PRP), and mesenchymal stem cell (MSC) therapy. RTs carry an excellent safety profile compared to IACSs. That shift in paradigm by moving away from using IACSs in OA to those RTs has shown more prolonged symptomatic effects, slowing or stopping the progression of OA and sometimes regeneration of the cartilage and surrounding tissues.

**Keywords:** Corticosteroid, Osteoarthritis, Degenerative, Hyaluronic Acid, Platelet-Rich Plasma, PRP, Mesenchymal Stem Cell, MSC, Regenerative.

### Introduction and Background

Osteoarthritis (OA) is the most common form of arthritis, the disease onset is varied, and the sequence of joint involvement and disease progression differs between individuals. Still, it commonly involves the knee and hip joints. The frequent symptoms of OA are joint pain, stiffness, joint swelling, restriction of joint movement, and functional limitations. Later, it can also lead to adjacent muscle wasting and weakness, poor balance, and joint deformities. OA holds marked unpredictability of disease manifestation and symptoms usually present in just one or a few joints in a middle-aged or older person. Predisposing factors to OA include ageing, inheritance, previous trauma, and obesity [1-3].

For management of knee and hip OA, various conservative treatment approaches are recommended, including non-pharmacological modalities; patient education, adjacent muscle exercises, weight control, walking aids, bracing, insoles adjustment, local cooling/heating, acupuncture, avoiding high impact activities, and electromagnetic treatment [4].

Oral medical therapies can be used like paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), opioids, and slow-acting alternative pills, namely combined glucosamine and chondroitin sulfate. If oral treatment is ineffective, we try intra-articular injections of corticosteroids (IACSs) combined with local anaesthesia [5,6].

Corticosteroids have a combination of anti-inflammatory and immune modulation effects. They directly target the nuclear steroid receptors and disrupt the inflammatory and immune cascade. This diminishes vascular permeability and inhibits the gathering of inflammatory cells, producing neutrophil superoxide, phagocytosis, metalloprotease, and averts the production of many inflammatory mediators like prostaglandin and leukotrienes [6,7]. The clinical effects are a reduction in the inflammation in acute or chronic synovitis such as swelling, heat, and tenderness and a rise in relative viscosity with an increment in hyaluronic acid concentration [7,8].

In randomized controlled trials in OA patients, there is proof that IACSs are helpful, but their advantage over placebo may be relatively short-lived, up to four weeks. In a Cochrane Review back in 2006 and other systemic reviews, the short-lived efficacy of IACSs in knee OA has been verified [5,9-11]. Additionally, the 2006 Cochrane Review has illustrated the scarcity of evidence for effectiveness in functional improvements like stiffness, quality of life, and walking distance with IACSs [5]. However, some literature revealed a possible advantage of up to 24 weeks [12].

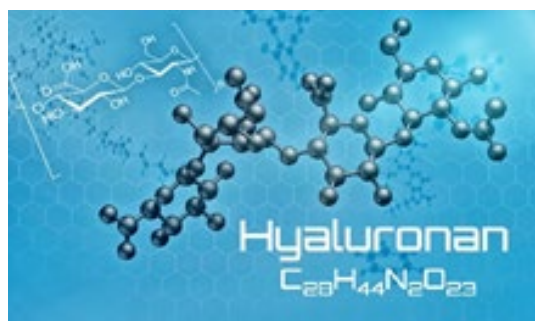
Various literature reports the possible complications of IACSs, including cartilage thinning with accelerated OA, subchondral insufficiency fracture, osteonecrosis [12,13], and a low frequency of joint infection [14]. The consensus of our management in OA is to control symptoms, improve function and quality of life, and reduce the disease progression to delay early joint replacement, which is sometimes not an option in patients with multiple comorbidities in the aged population. The benefit of steroid injections is short-lived. As science progresses, we need to experiment with new safe and effective therapies to develop them to the maximum level; thus, modern medicine is considering the new biological era of regenerative medicine.

### Summary of Emerging Novel Biologic Therapies

Weighing the risks and benefits of IACSs has led to a shift in the paradigm of using safe and effective intra-articular alternative biologic therapies, including hyaluronic acid, platelet-rich plasma, and mesenchymal stem cell (MSC) therapy with or without scaffolding techniques. The following is a brief description of the biological anti-osteoarthritis alternative therapies.

#### *Hyaluronic acid (HA) or hyaluronan*

HA or viscosupplementation is a natural anionic non-sulfated glycosaminoglycan (Figure 1) present in the cartilage matrix and synovial fluid (SF) component. Synoviocytes, chondrocytes, and fibroblasts produce HA and ooze it into the joint. HA augments the viscosity and elasticity of SF. SF with the usual HA concentration performs as a viscous lubricant throughout sluggish joint activities and as a resilient shock wave absorber during rapid joint activities [15].



**Figure 1:** Shows the complex structure of cross-linked Hyaluronan.

HA has multiple actions that constitute anti-inflammatory, painkiller, anabolic, and chondroprotective effects [16]. In OA pathology, the inflammation in the synovium leads to the enhanced permeability of the synovial coating for HA. Additionally, the raised SF levels of inflammatory cytokines, free radicals, and proteolytic enzymes in OA impair the function of HA and promote OA progression [17]; thus, in OA, the concentration and molecular weight of HA are diminished [18,19].

Although the exact in vivo mechanisms of action of HA are poorly understood in the joint, the intra-articular (IA) HA injection is thought to repair the viscoelastic properties of the medically altered SF. That's why we call this therapy viscosupplementation [17]. It is believed that HA transiently renovates the lubricating and shock-absorbing special effects of SF. Furthermore, various reports recommend that viscosupplements also have disease-modifying effects, such as the decline of inflammation in the synovium [20-24], safeguard opposed to cartilage erosion [25], and stimulation of IA HA manufacture [26]. Finally, HA has both direct and indirect analgesic activity inside the joints. The direct effect is through nociceptors inhibition and the lessened synthesis of substance P and bradykinin [27]. The indirect effect is via the anti-inflammatory properties of HA.

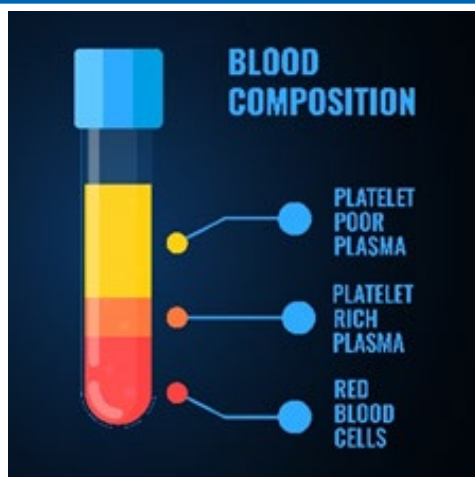
IA injection of HA is safe for knee OA [28,29]. The side effects are rare and local transient reactions in the injected joint with a reported incidence of 2-4% [30].

HA derived from biological fermentation, and those that have a molecular weight (MW) of  $\geq 3000$  kilodaltons (kDa) may determine greater efficacy in the management of knee OA [31]. Those called non-animal stabilized hyaluronic acid (NASHA) to avoid any allergic reaction to protein for the HA derived from the animal products.

In our experience, we favour the long-acting high MW cross-linked HA like durolane 100,000 kDa with a low degradation rate and a sound effect that can last between 26-52 weeks and sometimes longer [32,33].

#### *Platelet-rich plasma (PRP)*

PRP is derived from autologous blood by centrifugation process to extract a plasma solution (Figure 2) with significantly higher platelets concentration which could be as high as 4-5 times of the normal blood [34]. The platelets undertake the degranulation process to free growth factors (GFs). Platelets contain a lot of proteins that could reach more than 1100 different proteins, with many post-translational variations, developing in over 1500 protein-centered bioactive factors [35].



**Figure 2:** Shows Platelet-rich plasma (PRP) middle layer post blood centrifuging.

Various preparation techniques have been tried, including single versus double spinning, leucocyte-poor PRP(LP-PRP), leucocyte-rich PRP(LR-PRP), platelet-rich fibrin, and other filtration methods. Still, the optimum preparation is yet to be determined [36,37].

### What is the Mechanism of Action for PRP?

The platelet concentrate is stimulated by adding calcium chloride, resulting in the development of platelet gel and the release of GFs and bioactive particles. The common GFs are platelet-derived growth factor (PDGF), transforming growth factor (TGF)-beta, vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and epidermal growth factor (EGF) [38]. Those GFs are together with cytokines, chemokines, extracellular matrix proteins, prostaglandins, leukotrienes, and other active molecules to help the healing process [39,40]. These factors contribute to PRP's extensive roles in anti-inflammation by enhancing the expression of nuclear factor (NF)-kappa-beta inhibitor, chondrogenesis, bone remodelling, angiogenesis, and proliferation of mesenchymal stem cells, enhancing matrix synthesis, and the formation of collagen and cell differentiation [41-43].

Although PRP protocols are complex, the PRP mechanisms of action in a joint are still not answered fully [44]. LP-PRP is postulated to be more appropriate for intra-articular injection than leukocyte-rich PRP (LR-PRP) in the management of knee OA. When used for knee OA therapy, LP-PRP results in superior functional result scores contrasted with hyaluronic acid (HA) and placebo. LP-PRP and LR-PRP have similar safety profiles, although both produce more quick reactions than HA [45,46].

Our findings have been consistent with the literature; we summarize PRP results as easy, safe, not expensive, repeatable, and minimally invasive with sound effects. We noticed well in managing symptoms, reducing inflammation, and improving function and quality of life for up to one year [47]; we aim to slow OA's progression and delay an early joint replacement. Still,

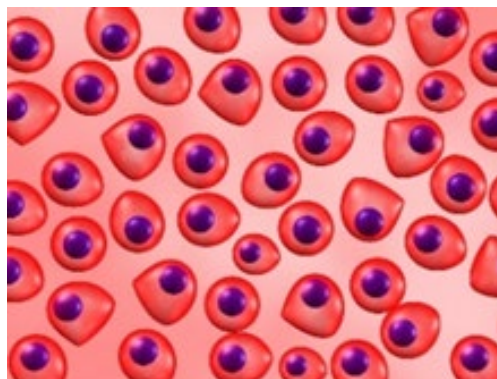
it does not rebuild the cartilage or meniscus, and the results are inconsistent. We found higher doses are more effective and reduce the frequency of the PRP injections, thus less exposure to repeat procedures and cheaper, and this has been reported in the literature [48].

PRP is more effective in comparative studies than intra-articular HA [49-51]. We use PRP alone or with soluble HA products for knee and hip OA in our practice. The literature supports that the combined PRP/HA injected has a more favourable outcome [52]. PRP is contraindicated in pregnancy and active cancer, especially haematologic malignancies because GFs can stimulate pre-existing cancer. PRP might not be effective in patients with significantly low platelets as there are not enough platelets to achieve the medical benefit.

We advise stopping non-steroidal anti-inflammatory drugs (NSAIDs) one week before and after the PRP injections; in addition, we recommend avoiding excessive alcohol intake for a few days after the procedure giving both NSAIDs and alcohol inhibit platelets function. Additionally, we try the limit and depth of local anaesthesia in the PRP injected area to reduce PRP's effect; we do not recommend local steroid injection mixing with PRP [53]. Taking a couple of paracetamol an hour before procedure and then regularly for a couple of days together with resting the area and brace use might help the recovery period and reduce the inflammatory healing response. The literature suggests good hydration might improve the outcome.

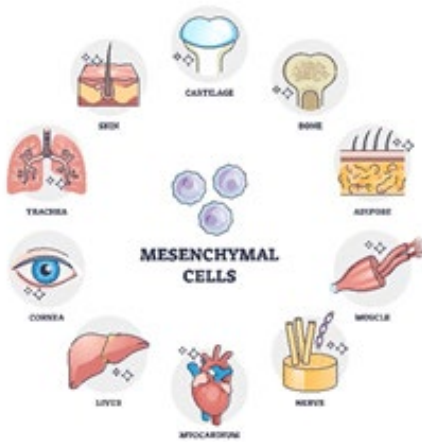
### Mesenchymal Stem Cell (MSC) Therapy

MSCs are primitive undifferentiated cells (Figure 3) that can differentiate into various types of cells (Figure 4) and proliferate indefinitely to produce more of the same stem cell. They are the earliest type of cell in a cell lineage [54]. They are found in both embryonic and adult organisms. Our article addresses adult multipotent MSC therapy even though pluripotent embryonic MSCs are more potent; we do not use them due to ethical reasons and the risk of malignancy, particularly teratoma [55]. We elected to use a safe approach autologous non-programmed adult MSC therapy derived from adipose tissues in our practice. Bone marrow aspirate/concentrate is also an effective treatment, but we only use fat-derived MSCs.



**Figure 3:** Shows undifferentiated mesenchymal stem cells.





**Figure 4:** Shows primary mesenchymal stem cells can differentiate to any cell type.

There are two approaches to autologous adipose-derived MSC therapy: The first one is the same day technique where the MSCs harvested by mini-liposuction procedure and then processed in a sterile fashion to get the final product called stromal vascular fraction (SVF), which then gets injected into the OA joint (s), with this approach is easy to do as one session, and it is done, but the downside with this approach is a low number of non-purified MSCs as no lab work is involved.

The other technique we use in our practice is called the expanded (culture) purified MSC therapy at an approved lab. The SVF will go into purification, sterilization, and expansion processes to reach a high number of purified MSCs. Still, it takes around 6-8 weeks to get the MSCs ready. The advantage of this approach is that the cells can be stored at -190 degrees using liquid nitrogen for up to 15 years or longer. The therapy can be repeated for severe cases such as booster doses, and the cells can be used for other degenerative or injured areas whenever needed.

In recent years, MSC therapy has changed the current therapeutic modality for OA by providing practice for repairing/regenerating cartilage. MSCs have the ability for self-renewal, multi-differentiation potential, limited immunogenicity, and easy nurturing and acquisition, making MSC therapy popular in clinical practice [56-58]. Additionally, their paracrine effect secretes various cytokines and growth factors, regulates the intra-articular microenvironment to anti-inflammatory properties, and stimulates chondrocytes to produce type II collagen, thus providing an aid for tissue repair [59,60]. The clinical efficacy and safety of intra-articular injection of MSCs in the treatment of OA have been comprehensively studied in multiple clinical trials [61-63]. Good clinical outcomes include pain relief, functional recovery, increased cartilage volume, and improved cartilage quality, particularly in large doses of MSCs [64].

Finally, various scaffolds other than PRP and HA have been used

to stimulate the MSCs, including collagen-based hydrogel and exosomes. Exosomes act like biologic garbage bins that carry proteins, lipids, mRNAs, non-coding RNAs, and even DNA out of cells [65]. Exosomes likewise enhance cell-cell communication [66]. Plasma and adipose-derived micro-RNA exosome particles can be used as a scaffolding technique to potentiate MSC therapy. The Contraindications of MSC therapy are similar to PRP.

Our expanded (culture) MSC technique starts with fat harvesting through mini-liposuction; we wash the lipo-aspirate and then digest it with 0.2 U/mL collagenases. The SVF get separated from the digested adipose tissue through density centrifugation. The SVF was then plated down and cultured in our specialized biological lab using Dulbecco's Modified Eagle Medium (DMEM) and 10% human platelet lysate (HPL) to expand the MSCs population. Cells grow to at least 90% confluency over 6-8 weeks and are cryopreserved until injection. During the lab process, the MSCs get purified, sterilized using antimicrobial/antifungal agents (penicillin, streptomycin and amphotericin B), and expanded according to an approved protocol. Injections get prepared on the treatment date; the cells get washed and filtered before being resuspended in Hartmann's solution with 10% HPL in syringes for administration. Cell count was measured manually and confirmed by a hemocytometer, and the viability of the MSCs gets measured by trypan blue exclusion dye. Our doses vary, but they can be 10-100 x 10<sup>6</sup> per joint with or without PRP. Generally speaking, we use concentrated MSCs to avoid dilution with PRP, and for medium-large joints, we mix MSCs with PRP in the same syringe. Sometimes we add soluble HA, and all procedures are done under ultrasound guidance to ensure the maximum concentration of the injectate. We have tried adding plasma exosomes in an experimental trial with good symptomatic relief. We have reasonable clinical and radiological evidence of improvements in OA of the knee, hip, hand, and ankle joints [67-71]; additionally, we found that expanded MSC therapy is also effective for tendon repairs [72,73].

## Conclusion

Regenerative therapy is the future medicine and might replace mainstream surgery if used appropriately early in the disease process; this option is favourable over transient symptoms control by corticosteroid injections with possible adverse chondrogenic effects. Regenerative therapy of hyaluronic acid, platelet-rich plasma and mesenchymal stem cell therapy is a novel experimental modality with an anabolic effect in treating symptoms in orthopaedic conditions. We need to develop those therapies and more randomized controlled trials to confirm the consistency of those findings in regenerative medicine.

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## Competing Interests

The author has declared that no competing interests exist.

## References

1. Losina E, Weinstein AM, Reichmann WM, et al. (2013) Lifetime risk and age at diagnosis of symptomatic knee osteoarthritis in the US. *Arthritis Care Res (Hoboken)* 65(5):703-711.
2. Loeser RF (2009) Aging and osteoarthritis: the role of chondrocyte senescence and aging changes in the cartilage matrix. *Osteoarthritis Cartilage* 17:971-979.
3. Loeser RF, Goldring SR, Scanzello CR et al. (2012) Osteoarthritis: a disease of the joint as an organ. *Arthritis Rheum* 64:1697-1707.
4. Jevsevar DS, Brown GA, Jones DL, Matzkin EG, Manner PA, et al. (2013) The American Academy of Orthopaedic Surgeons evidence-based guideline on: Treatment of osteoarthritis of the knee, 2nd edition. *J Bone Joint Surg Am* 95:1885-1886.
5. Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G. (2006) Intraarticular corticosteroid for treatment of osteoarthritis of the knee. *Cochrane Database Syst Rev* (2):CD005328.
6. Creamer P (1999) Intra-articular corticosteroid treatment in osteoarthritis. *Curr Opin Rheumatol* 11:417-421.
7. Ostergaard M, Halberg P (1998) Intra-articular corticosteroids in arthritic disease: a guide to treatment. *BioDrugs* 9:95-103.
8. Jessar Ra, Ganzell Ma, Ragan C (1953) The action of hydrocortisone in synovial inflammation. *J Clin Invest* 32:480-482.
9. Chao J, Wu C, Sun B, Hose MK, Quan A, et al. (2010) Inflammatory characteristics on ultrasound predict poorer longterm response to intraarticular corticosteroid injections in knee osteoarthritis. *J Rheumatol* 37:650-655.
10. Hepper CT, Halvorson JJ, Duncan ST, Gregory AJ, Dunn WR, et al. (2009) The efficacy and duration of intra-articular corticosteroid injection for knee osteoarthritis: a systematic review of level I studies. *J Am Acad Orthop Surg* 17:638-646.
11. Kruse DW (2008) Intraarticular cortisone injection for osteoarthritis of the hip. Is it effective? Is it safe? *Curr Rev Musculoskelet Med* 1(3-4):227-233.
12. Arroll B, Goodyear-Smith F (2004) Corticosteroid injections for osteoarthritis of the knee: meta-analysis. *BMJ* 328:869.
13. Andrew J Kompel, Frank W Roemer, Akira M Murakami, Luis E Diaz, Michel D Crema, et al. (2019) Intra-articular Corticosteroid Injections in the Hip and Knee: Perhaps Not as Safe as We Thought?. *Radiology* 293:656-663.
14. Petersen SK, Hansen I, Andreassen RA (2019) Low frequency of septic arthritis after arthrocentesis and intra-articular glucocorticoid injection. *Scand J Rheumatol* 48(5):393.
15. Brockmeier SF, Shaffer BS (2006) Viscosupplementation therapy for osteoarthritis. *Sports Med Arthrosc* 14:155-162.
16. Axe JM, Snyder-Mackler L (2013) The role of viscosupplementation. *Sports Med Arthrosc* 21:18-22.
17. Balazs EA, Denlinger JL (1993) Viscosupplementation: a new concept in the treatment of osteoarthritis. *J Rheumatol Suppl* 39:3-9.
18. Moreland LW (2003) Intra-articular hyaluronan (hyaluronic acid) and hylans for the treatment of osteoarthritis: mechanisms of action. *Arthritis Res Ther* 5:54-67.
19. Wattersson JR, Esdaile JM (2000) Viscosupplementation: therapeutic mechanisms and clinical potential in osteoarthritis of the knee. *J Am Acad Orthop Surg* 8:277-284.
20. Wang Y, Hall S, Hanna F, Wluka AE, Grant G, et al. (2011) Effects of Hylan G-F 20 supplementation on cartilage preservation detected by magnetic resonance imaging in osteoarthritis of the knee: a two-year single-blind clinical trial. *BMC Musculoskelet Disord* 12:195.
21. Bagga H, Burkhardt D, Sambrook P, March L (2006) Longterm effects of intraarticular hyaluronan on synovial fluid in osteoarthritis of the knee. *J Rheumatol* 33:946-950.
22. Listrat V, Ayral X, Patarnello F, Bonvarlet JP, Simonnet J, et al. (1997) Arthroscopic evaluation of potential structure modifying activity of hyaluronan (Hyalgan) in osteoarthritis of the knee. *Osteoarthritis Cartilage* 5:153-160.
23. Pasquali Ronchetti I, Guerra D, Taparelli F, Boraldi F, Bergamini G, et al. (2001) Morphological analysis of knee synovial membrane biopsies from a randomized controlled clinical study comparing the effects of sodium hyaluronate (Hyalgan) and methylprednisolone acetate (Depomedrol) in osteoarthritis. *Rheumatology (Oxford)* 40:158-169.
24. Guidolin DD, Ronchetti IP, Lini E, Guerra D, Frizziero L (2001) Morphological analysis of articular cartilage biopsies from a randomized, clinical study comparing the effects of 500-730 kDa sodium hyaluronate (Hyalgan) and methylprednisolone acetate on primary osteoarthritis of the knee. *Osteoarthritis Cartilage* 9:371-381.
25. Wenz W, Breusch SJ, Graf J, Stratmann U (2000) Ultrastructural findings after intraarticular application of hyaluronan in a canine model of arthropathy. *J Orthop Res* 18:604-612.
26. Pozo MA, Balazs EA, Belmonte C (1997) Reduction of sensory responses to passive movements of inflamed knee joints by hylan, a hyaluronan derivative. *Exp Brain Res* 116:3-9.
27. Gomis A, Miralles A, Schmidt RF, Belmonte C (2009) Intra-articular injections of hyaluronan solutions of different elastoviscosity reduce nociceptive nerve activity in a model of osteoarthritic knee joint of the guinea pig. *Osteoarthritis Cartilage* 17:798-804.
28. Divine JG, Shaffer MD (2011) Use of viscosupplementation for knee osteoarthritis: an update. *Curr Sports Med Rep* 10:279-284.
29. Becker LC, Bergfeld WF, Belsito DV, Klaassen CD, Marks JG, et al. (2009) Final report of the safety assessment of hyaluronic acid, potassium hyaluronate, and sodium hyaluronate. *Int J Toxicol* 28:5-67.
30. Adams ME, Lussier AJ, Peyron JG. (2000) A risk-benefit assessment of injections of hyaluronan and its derivatives in the treatment of osteoarthritis of the knee. *Drug Saf* 23:115-130.

31. Altman RD, Bedi A, Karlsson J, Sancheti P, Schemitsch E (2016) Product differences in intra-articular hyaluronic acids for osteoarthritis of the knee. *Am J Sports Med* 44(8):2158-2165.
32. David Webner, Yili Huang, Charles D (2021) Hummer Intraarticular Hyaluronic Acid Preparations for Knee Osteoarthritis: Are Some Better Than Others?. *Cartilage* 13(1):1619S-1636S.
33. Leighton, R, Fitzpatrick, J, Smith, H, Crandall, D, Flannery, CR, et al. (2018) Systematic clinical evidence review of NASHA (durolane hyaluronic acid) for the treatment of knee osteoarthritis. *Open Access Rheumatol.* 10:43-54.
34. Hall MP, Band PA, Meislin RJ, Jazrawi LM, Cardone DA (2009) Platelet-rich plasma: current concepts and application in sports medicine. *J Am Acad Orthop Surg* 17:602-608.
35. Boswell SG, Cole BJ, Sundman EA, Karas V, Fortier LA (2012) Platelet-rich plasma: a milieu of bioactive factors. *Arthroscopy* 28:429-439.
36. Andia I, Maffulli N (2013) Platelet-rich plasma for managing pain and inflammation in osteoarthritis. *Nat Rev Rheumatol* 9:721-730.
37. Dohan Ehrenfest DM, Rasmusson L, Albrektsson T (2009) Classification of platelet concentrates: from pure platelet-rich plasma (P-PRP) to leucocyte- and platelet-rich fibrin (L-PRF) *Trends Biotechnol* 27:158-167.
38. Xuetao Xie, Changqing Zhang, Rocky S Tuan (2014) Biology of platelet-rich plasma and its clinical application in cartilage repair. *Arthritis Research & Therapy* 16(1): 204.
39. Pietrzak WS, Eppley BL (2005) Platelet rich plasma: biology and new technology. *J Craniofac Surg* 16:1043-1054.
40. Anitua E, Andia I, Ardanza B, Nurden P, Nurden AT (2004) Autologous platelets as a source of proteins for healing and tissue regeneration. *Thromb Haemost* 91:4-15.
41. Drengk A, Zapf A, Stürmer EK, Stürmer KM, Frosch KH (2009) Influence of platelet-rich plasma on chondrogenic differentiation and proliferation of chondrocytes and mesenchymal stem cells. *Cells Tissues Organs* 189:317-326.
42. Woodall J, Tucci M, Mishra A, Benghuzzi H (2007) Cellular effects of platelet rich plasma: a study on HL-60 macrophage-like cells. *Biomed Sci Instrum* 43:266-271.
43. Andia I, Maffulli N (2013) Platelet-rich plasma for managing pain and inflammation in osteoarthritis. *Nat Rev Rheumatol* 9(12):721-30.
44. Zhu Y, Yuan M, Meng HY, Wang AY, Guo QY, et al. (2013) Basic science and clinical application of platelet-rich plasma for cartilage defects and osteoarthritis: a review. *Osteoarthritis Cartilage* 21:1627-1637.
45. Jonathan C Riboh, Bryan M Saltzman, Adam B Yanke, Lisa Fortier, Brian J Cole (2016) Effect of Leukocyte Concentration on the Efficacy of Platelet-Rich Plasma in the Treatment of Knee Osteoarthritis. *Meta-Analysis Am J Sports Med* 44(3):792-800.
46. Steven Sampson, Marty Reed, Holly Silvers, Michael Meng, Bert Mandelbaum (2010) Injection of platelet-rich plasma in patients with primary and secondary knee osteoarthritis: a pilot study. *Clinical Trial Am J Phys Med Rehabil* 89(12):961-969.
47. Bennell KL, Hunter DJ, Paterson KL (2017) Platelet-Rich Plasma for the Management of Hip and Knee Osteoarthritis. *Curr Rheumatol Rep* 19(5):24.
48. Caroline Guillibert, Caroline Charpin, Marie Raffray, et al. (2019) Single Injection of High Volume of Autologous Pure PRP Provides a Significant Improvement in Knee Osteoarthritis: A Prospective Routine Care Study. *Int J Mol Sci* 20(6): 1327.
49. Spaková T, Rosocha J, Lacko M, Harvanová D, Gharaibeh A (2012) Treatment of knee joint osteoarthritis with autologous platelet-rich plasma in comparison with hyaluronic acid. *Am J Phys Med Rehabil* 91:411-417.
50. Kon E, Mandelbaum B, Buda R, Filardo G, Delcogliano M, et al. (2011) Platelet-rich plasma intra-articular injection versus hyaluronic acid viscosupplementation as treatments for cartilage pathology: from early degeneration to osteoarthritis. *Arthroscopy* 27:1490-1501.
51. Say F, Gürler D, Yener K, Bülbül M, Malkoc M (2013) Platelet-rich plasma injection is more effective than hyaluronic acid in the treatment of knee osteoarthritis. *Acta Chir Orthop Traumatol Cech* 80:278-283.
52. Wenxing Yu, Peng Xu, Guiling Huang, and Lin Liu (2018) Clinical therapy of hyaluronic acid combined with platelet-rich plasma for the treatment of knee osteoarthritis. *Exp Ther Med* 16(3): 2119-2125.
53. Bradley Carofino, David M Chowanec, Mary Beth McCarthy, James P Bradley, Steve Delaronde, et al. (2012) Corticosteroids and local anesthetics decrease positive effects of platelet-rich plasma: an in vitro study on human tendon cells. *Arthroscopy* 28(5):711-9.
54. Atala A, Lanza R (2012) *Handbook of Stem Cells*. Academic Press. p. 452. ISBN 978-0-12-385943-3.
55. Hannes Hentze, Poh Loong Soong, Siew Tein Wang, Blaine W Phillips, Thomas C Putti, et al. (2009) Teratoma formation by human embryonic stem cells: evaluation of essential parameters for future safety studies. *Stem Cell Res* 2(3):198-210.
56. Kim SH, Ha CW, Park YB, et al. (2019) Intra-articular injection of mesenchymal stem cells for clinical outcomes and cartilage repair in osteoarthritis of the knee: a meta-analysis of randomized controlled trials. *Arch Orthop Trauma Surg* 139:971-980.
57. Lee WS, Kim HJ, Kim KI, et al. (2019) Intra-articular injection of autologous adipose tissue-derived mesenchymal stem cells for the treatment of knee osteoarthritis: a phase iib, randomized, placebo-controlled clinical trial. *Stem Cells Transl Med* 8:504-511.
58. Xia P, Wang X, Lin Q, et al. (2015) Efficacy of mesenchymal stem cells injection for the management of knee osteoarthritis: a systematic review and metaanalysis. *Int Orthop* 39:2363-2372.
59. Lu L, Dai C, Zhang Z, et al. (2019) Treatment of knee osteoarthritis with intraarticular injection of autologous

- adipose-derived mesenchymal progenitor cells: a prospective, randomized, double-blind, active-controlled, phase IIb clinical trial. *Stem Cell Res Ther* 10:143.
60. Migliorini F, Rath B, Colarossi G, et al. (2019) Improved outcomes after mesenchymal stem cells injections for knee osteoarthritis: results at 12- months follow-up: a systematic review of the literature. *Arch Orthop Trauma Surg* 2019.
  61. Centeno CJ, Al Sayegh H, Freeman MD, Smith J, Murrell WD, et al. (2018) A multi-center analysis of adverse events among two thousand, three hundred and seventy-two adult patients undergoing adult autologous stem cell therapy for orthopaedic conditions. *Int Orthop* 40:1755-1765.
  62. Bastos R, Mathias M, Andrade R, Raquel Bastos, Alex Balduino, et al. (2018) Intra-Articular injections of expanded mesenchymal stem cells with and without addition of platelet-rich plasma are safe and effective for knee osteoarthritis. *Knee Surg Sports Traumatol Arthrosc* 26:3342-3350.
  63. Brown MH, Scholes C, Hafsi K, Marenah M, Li J, et al. (2019) Efficacy and safety of culture-expanded, mesenchymal stem/stromal cells for the treatment of knee osteoarthritis: a systematic review. *J Orthop Surg Res* 14:34.
  64. Chris Hyunchul Jo, Young Gil Lee, Won Hyoung Shin, Hyang Kim, Jee Won Chai, et al. (2014) Intra-articular injection of mesenchymal stem cells for the treatment of osteoarthritis of the knee: a proof-of-concept clinical trial. *Stem Cell* 32(5):1254-1266.
  65. Chao Han, Xuan Sun, Ling Liu, Haiyang Jiang, Yan Shen, et al. (2016) Exosomes and Their Therapeutic Potentials of Stem Cells. *Stem Cell International* 2016:7653489.
  66. Xiaowen Wu, Junxiang Su, Jizhen Wei, Nan Jiang, and Xuejun Ge (2021) Recent Advances in Three-Dimensional Stem Cell Culture Systems and Applications. *Stem Cells International* 2021: 9477332.
  67. Hassan Mubark (2021) Resolution of Patellofemoral Bone Marrow Edema and Subchondral Cysts on MRI Post a Single Autologous Fat-Derived Expanded Mesenchymal Stem Cell Therapy. *Adv Ortho and Sprts Med: AOASM-151*.
  68. Hassan Mubark (2021) Efficacy and Safety of Expanded Stem Cell Therapy and Platelet-Rich Plasma in Partial Knee Replacement: A Case Report. *Adv Ortho and Sprts Med: AOASM-163*.
  69. Hassan Mubark (2022) Remarkable pain control and functional improvement in clubfoot-related ankle osteoarthritis post autologous expanded mesenchymal stem cell therapy. *Medical & Clinical Research* 7(3):34-37.
  70. Hassan Mubark (2021) Persistent Symptomatic and Functional Improvement of Hands Osteoarthritis Post-Autologous Expanded Mesenchymal Stem Therapy: Case Report. *Adv Ortho and Sprts Med: AOASM-154*.
  71. Hassan Mubark (2021) Complete Resolution of Extensive Labral tear and Para-labral Cysts on MRI Following 3D Collagen-Based Stem Cell Therapy in Dysplastic Hip: Case Report. *Adv Ortho and Sprts Med AOASM-157*.
  72. Hassan Mubark (2020) Regeneration of full-thickness supraspinatus rotator cuff tendon tear after treatment with autologous mesenchymal stem cells. *Bio Ortho J* 2 (1).
  73. Hassan Mubark (2021) Successful Treatment with Autologous Mesenchymal Stem Cells Therapy for Muscle Wasting Post-Surgical Repair of Achilles Tendon: A Case Report. *Adv Ortho and Sprts Med: AOASM-145*.

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