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The breakthroughs and barriers to clinical utilization of *in vivo* cellular therapies in the management of osteoarthritis in humans: A review

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Abstract
Osteoarthritis is a debilitating illness that is commonly characterized by swelling, pain, stillness and limited function of the joints. It is a degenerative disease that has affected over 7% of the world's population and is responsible for over 2% of all DALYs. It is one of the most common clinical presentations and the most common joint pathology among adults. From non-pharmacological, to pharmacological and even surgical modalities, there are a myriad of therapies for its symptomatic treatment, but no cure. Advances in research for a cure have started exploring molecular mechanisms, such as genetics and regenerative medicine. Regenerative medicine focuses on stem cellular harvest, transplants and manipulations. Sources of MSC are currently BMSC and ADSC. Application of this therapy have moved from an invasive approach to a non-invasive approach. Recent advances in stem cell therapies have focused on MSCs, EVs and exosomes, for their effective and promising results so far. As thousands of more case studies and researches are currently going on around the world, this study will be taking a systematic look in to the breakthroughs and barriers these researchers have discovered or encountered in the course of their research and how this affects the propensity to clinical adoption and utilization of stem cellular therapies in the treatment of osteoarthritis.

Keywords: MSC, BMSC, ADSC

1. Introduction
The global burden of osteoarthritis (OA) has been on a progressive increase, currently affecting approximately 7% of the world's population [1]. The Disability Adjusted Life Years (DALYs) associated with OA affects approximately 2% of the world's human population [1-2]. Although the global burden of disease is most significant in high and higher-middle income countries, the prevalence in lower-middle- and low-income countries are now witnessing a significant rise. These lower economic countries also have factors such as poor health facilities and other social determinants, thus propagating a worse burden of disease and DALYs [1-3]. In fact, the true burden of OA is actually underestimated [1-2].
However, many people consider it a physiologic path of aging, and not a real disease pathology of its own [6]. In fact, it is not featured in the global strategic plans for non-communicable diseases [4]. This mentality is also shared by practitioners, as patients have reported varying levels of neglect and down-play of their genuine concerns and complains [5]. This abandon in combination with varying levels of therapeutic nihilism on the path of the medical professionals, worsens the personal, economic and social tolls these patients have to bear [4]. One might wonder if this abandon is the reason for positive progress in the management of OA not making as much head-way as treatments of other musculoskeletal diseases and chronic pathologies or, if this slow progress is the reason for the abandon on the side of the health professionals [3, 6]. Nevertheless, with a myriad of treatment options, some of which are not so therapeutically significant, the financial and pathological burden are bore by often ill-informed patients [7-9]. Notwithstanding, tremendous progress has been made in the public health understanding of the disease, the global burden and pathogenesis of the disease [10].

However, as regards an effective mode of treatment and management, a myriad of non-pharmacological, pharmacological and surgical treatments are available, but no cure yet [11]. In clinical practice, commonly used therapies such as non-steroidal anti-inflammatory drugs and glucocorticoids have moderate effectiveness with substantial side effects on the long run [12-13]. Recent strategies have tried hydroxychloroquine (HC) but several studies have failed to produce effective satisfactory results [14-15]. A lot of researches are still going, such as genetic studies that have made significant findings in the genomic risk factors of OA [16-17]; the anabolic BMP-7 and anti-catabolic MMP-13 inhibitor drug trials [18-19]. Regenerative cellular therapies (BMSC, ADSC and MSC) and so on [20-22].

Discussion

Regenerative therapies have shown a lot of promise from multiple case studies being carried out around the world. It utilizes transplanted Stem cells to help in regeneration of the damaged area. Stem cells may be acquired from bone marrow (BMSC) and adipocytes (ADSC), and other areas rich in mesenchymal stem cells (MSC). Unlike initially, when transplantation used to be via invasive surgery, it is now transplanted autologous via intra-articular injections [23-24]. This studies on MSC utilization in human trial have shown effective results.

When MSC is transplanted into the joint compartment it elicits an immunomodulatory and chondroprotective effect that lasts a while, leading to a cascade of activities. These actions are mediated in a paracrine manner [25]. Exposure to inflammatory signals develop and promotes secretions from the MSC [26]. It produces Extracellular Vehicles (EVs), which basically are small phospholipid-bilayer-enclosed particles carrying many cytoplasmic components [27-28]. In the body, EVs play numerous roles, metabolic and mRNA transcription roles [29]. Amongst the EVs, exosomes are the most therapeutically palatable so far, and hence the most studied [30]. Consensus of studies carried out on MSC, EVs and exosomes applied for treatment of cartilage pathologies and knee osteoarthritis had promising positive effects [46].

Understanding these mechanisms, more purified studies utilizing EVs were done. These studies have been conducted on an *in vitro* and *in vivo* level. *In vitro*, properties such as anti-catabolic, immunomodulatory and regenerative properties were assigned to EVs and secretomes. While on *in vivo* pre-clinical application, studies showed that there were positive effects on the joint and confirmed effectiveness of EV injections as a minimally invasive therapy [32]. Furthermore, when exosomes were used in an animal-based study, they improved the gait abnormality patters in OA and MSC secretomes provided early pain reduction [33-34]. It has proven to be an ever-advancing field.

Furthermore, more breakthroughs have been seen in understanding the knowledge and future prospects that mesenchymal based therapy may hold. In fact, the promise EVs have shown also distinguishes them as promising potential next-generation biomarkers to predict the pathophysiological state of the joint [46]. Hence, the role of cellular therapies in even OA primary prevention and assessment. More studies are currently being conducted on its potentials in the management of other forms of arthritis, such as rheumatic arthritis. The adoption of intra-articular form of transplantation from an initial invasive surgical method, the sequestration of stem cells from adipose tissues and focused therapies that have isolation and utilization of EVs and exosomes are very significant breakthrough in yet [21, 23, 33-34]. Although, studies have identified some modifiable and non-modifiable characteristics and barriers to effective utilization of MSC therapies, such as age, gender and oxygen concentration (Normoxic vs. hypoxic) conditions which may affect cell proliferation and regeneration in varying degrees [35-36]. A pilot study that quantitatively assessed the barriers to clinical development and adoption of cellular therapies found that the major barriers that existed were cost-effectiveness, efficacy, reimbursement and regulations. The study also went further to suggest future studies answering questions of regulators, as well as a broader clinical community [37], the promising potentials shown by stem cell therapies are still palpable.

Conclusion

However, with so many concurrent studies being carried out on stem cell therapies all around the world, with a lot of significant studies not even being published, it is hard to keep detailed track of the milestones each researcher is attaining [22]. We need to also understand the progress and observations made in case control trials that have attempted to utilize these therapies in human based trials. As the end game is to aim towards clinical utilization of the cellular therapies in order to provide evidence based and improved management options to alleviate the burden of disease and DALYs experienced by OA patients. There is thus a need to have a directory or a study that aims at streamlining and properly classifying for sake of research, clinical application and learning, the essential studies and findings as regards *in vivo* utilization of cellular therapies in OA.

Conflict of interest

The Author's declares no conflict of interest.

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References

1. Hunter DJ, March L, Chew M. Osteoarthritis in 2020 and beyond: A Lancet Commission. The Lancet. 2020 Nov 28;396(10264):1711-2. https://doi.org/10.1016/S0140-6736(20)32230-3. Accessed December 11, 2021.
2. Davies BM, Khan WS. Stem cell therapy in orthopedics. Orthopedics of the upper and lower limb, c2020, p. 565-572. https://doi.org/10.1007/978-3-030-43286-7_32 Online ISBN: 978-3-030-43286-7. Accessed December 31, 2021.
3. Grassel S, Muschter D. Recent advances in the treatment of osteoarthritis. Version 1. F1000Res. 2020;9:F1000. Faculty rev-325. DOI: https://doi.org/10.12688.f1000research.22115.1 Accessed December 30, 2021.
4. Ranmuthu CDS, Ranmuthu CKI, Khan WS. Evaluating the current literature on treatment containing adipose derived stem cells for osteoarthritis: a progress update. Curr Rheumatol Rep. 2018;20:67.

https://doi.org/10.1007/s11926-018-0776-7 Accessed December 31, 2021.
5. Global Burden of Disease Collaborative Network Global Burden of Disease Study (GBD 2019) results. c2019. http://ghdx.healthdata.org/gbd-results-tool Accessed December 28th, 2021.
6. Global burden of disease collaborative network. Global burden of disease study (GBD 2019) results. c2019. Osteoarthritis-level 3 cause. https://www.healthdata.org/results/gbd_summaries/2019/osteoarthritis-level-3-cause Accessed December 28th, 2021
7. Luong ML, Cleveland RJ, Nyrop KA, Callahan LF. Social determinants and osteoarthritis outcomes. Aging health. 2012;8(4):413-437. https://doi.org/10.2217/ahe.12.43 Accessed December 28th, 2021.
8. Veronese N, Cereda E, Maggi S, Luchini C, Solmi M, Smith T, *et al*. Osteoarthritis and mortality: A prospective cohort study and systematic review with meta-analysis. Semin Arthritis Rheum. 2016;46(2):160-167. https://doi.org/10.1016/j.semarthrit.2016.94.002. Accessed December 28th, 2021.
9. Alami S, Boutron I, Desjeux D, Hirschhorn M, Meric G, Rannou F, *et al*. patients' and practitioner's views of knee osteoarthritis and its management: A qualitative interview study. PloS One. 2011;6(5):e19634. https://doi.org/10.1371/journal.pone.0019634
10. Hagen KB, Smedslund G, Osteras N, Jamtvedt G. Quality of community-based osteoarthritis care: A systematic review and meta-analysis. Athritis care Res (Hoboken). 2016;68(10):1443-1452. https://doi.org/10.1002/acr.22891 Accessed December 31, 2021
11. Hunter DJ. Osteoarthritis management: time to check the deck. J Orthop Sports Phys Ther. 2017;47(6):370-372. https://dooi.org/10.2519/jospt.2017.0605. Accessed December 11, 2021
12. Bannuru RR, Osani MC, Vaysbrot EE, Arden NK, Bennell K, Bierma-Zeinstra SMA, *et al*. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. Osteoarthritis Cartilage. 2019;27(11):1578-1589. https://doi.org/10.1016/j.joca.2019.06.011. Accessed December 31, 2021
13. Basedow M, Esterman A. Assessing appropriateness of osteoarthritis care using quality indicators: A systematic review. J Eval Clin Pract. 2015;21(5):782-789. https://doi.org/10.1111/jep.12402. Accessed December 11, 2021
14. Hunter DJ, March L, Chew M. Osteoarthritis in 2020 and beyond: A lancet commission. Lancet. 2020;396(10264):1711-1712. https://doi.org/10.1016/S0140-6736(20)32230-3. Accessed December 11, 2021
15. Anandacoomarasamy A, March L. Current Evidence for osteoarthritis treatments. Ther Adv Musculoskelet Dis. 2010 Feb;2(1):17-28. Doi: https://doi.org/10/1177/1759720X09359889. Accessed on December 30, 2021
16. Pelletier JP, Martel-Pelletier J, Rannou F, Cooper C. Efficacy and safety of oral NSAIDs and analgesics in the management of osteoarthritis: Evidence from real-life setting trials and surveys. Semin Arthritis Rheum. 2016 Feb;45(4):S22-S27. Doi: https://doi.org/10.1016/j.semarthrit.2015.11.009
17. Savvidou O, Milonaki M, Goumenos S, Flevas D, Papagelopoulos P, Moutsatsou P. Glucocorticoid signaling and osteoarthritis. Mol Cell Endocrinol. 2019;480():153-66. Doi: https://doi.org/10.1016/j.mce.2018.11.001
18. Lee W, Ruijgrok L, Klerk BB, Kok MR, Kloppenburg M, Gerards S. Efficacy of hydroxychloroquine in hand osteoarthritis: A randomized, double-blind, placebo-controlled trial. Arthritis Case Res (Hoboken). 2018;70(9):1320-5. Doi: https://doi.org/10.1002/acr.23471
19. Kingsbury Sr, Tharmanathan P, Keding A, Ronaldson SR, Grainger A, Wakefield RJ, *et al*. Hydroxychloroquine effectiveness in reducing symptoms of hand osteoarthritis: A randomized trial. Ann intern Med. 2018;168(6):385-95. Doi: https://doi.org/10.7326/M17-1430
20. Tachamazidou I, Hatzikotoulas K, Southam L, Esparza-Gordillo J, Haberland V, Zheng J, *et al*. arc OGEN Consortium. Identification of new therapeutic targets for osteoarthritis through genome wide analusses OD UK biobank data. Nat. Genet. 2019;51(2):230-236. Doi: https://doi.org/10.1038/s41588-018-0327-1 Accessed December 30th, 2021.
21. Boer CG, Hatzikotoulas K, Southam L, Van Meurs JB, Stykarsdottir U, Zeggini E, *et al*. Deciphering osteoarthritis genetics across 826, 690 individuals from 9 populations. Cell press. 2021 Aug;184(18):P4784-4818.E17. doi: https://doi.org/10.1016/j.cell/2021.07.038 Accessed December 30th, 2021.
22. Evans CH, Kraus VB, Setton LA. Progress in intra-articular therapy. Nat Rev Rheumatol. 2014;10(1):11-22. Doi: https://doi.org/10.1038/nrrheum.2013.159 Accessed December 30th, 2021.
23. Tonge DP, Pearson MJ, Jones SW. The hallmarks of osteoarthritis and the potential to develop personalized diseases-modifying pharmacological therapeutics. Osteoarthritis Cartilage. 2014;22(5):609-21. Doi: https://doi.org/10.1016/j.joca.2014.04.004 Accessed December 30th, 2021.
24. Davies BM and Khan WS. Stem cell therapy in orthopedics. Orthopedics of the upper and lower limb. 2020, p. 565-572. https://doi.org/10.1007/978-3-030-43286-7_32 online ISBN: 978-3-030-43286-7. Accessed December 31, 2021.
25. Ranmuthu CDS, Ranmuthu CKI, Khan WS. Evaluating the current literature on treatment containing adipose derived stem cells for osteoarthritis: A progress update. Curr Rheumatol Rep. 2018;20(11):67. https://doi.org/10.1007/s11926-018-0776-7 Accessed December 31, 2021.
26. Grassel S, Muschter D. Recent advances in the treatment of osteoarthritis. Version 1. F1000Res. 2020;9(1):F1000 Faculty rev-325. Doi: https://doi.org/10.12688.f1000research.22115.1 Accessed December 30, 2021.
27. Roubille C, Pelletier JP, Martel-Pelletier J. New and emerging treatments for osteoarthritis management: will the dream come true with personalized medicine? Expert Opin Pharmacother. 2013;14(15):2059-77. Doi: https://doi.org/10.1517/14656566.2013.825606 Accessed December 30th, 2021.
28. Freitag J, Bates D, Wickham J, Shah K, Huguenin L, Tenen A, *et al*. Adipose-derived mesenchymal stem cell

therapy in the treatment of knee osteoarthritis: A randomized controlled trial. Regenerative medicine. 2019 Feb;14(3):213-230. https://doi.org/10.2217/rme-2018-0161 Accessed December 31, 2021.
29. Mancuso P, Raman S, Glynn A, Barry F and Murphy MJ. Mesenchymal Stem cell therapy for osteoarthritis: the critical role of the cell secretomes. Front. Biotechnol. 2019;29:7-9. Doi: https://doi.org/10.3389/fbioe.2019.00009 Accessed December 30th, 2021.
30. Lee MJ, Kim J, Kim MY, Bae YS, Ryu SH, Lee TG, *et al*. Proteomic analysis of tumor necrosis factor-a-induced secretomes of human adipose tissue-derived mesenchymal stem cells. J Proteome Res. 2010;9(4):1754-62. Doi: https://doi.org/10.1021/pr900898n Accessed December 30th, 2021.
31. Sukmawati Tansil Tan, Yohanes Firmansyah, Jessica Elizabeth. New approach to skin burn treatment: Potential of Secretome from Wharton's jelly Mesenchymal stem cell therapy. Int. J Adv. Biochem. Res. 2020;4(2):11-16. DOI: 10.33545/26174693.2020.v4.i2a.49
32. Riazifar M, Pone EJ, Lotvall J, *et al*. Sem Cell extracellular vesicles: Extended messages of regeneration. Annu Rev Pharmacol Toxicol. 2017 Jan;57:125-54. DOI: https://doi.org/10.1146/annurev-pharmtox-061616-030146 Accessed December 30th, 2021.
33. Gyorgy B, Szabo TG, Pasztoi M, *et al*. Membrane vesicles, current state-of-the-art: emerging role of extracellular vesicles. Cell Mol Life Sci. 2011;68(16):2667-88. DOI: https://doi.org/10.1007/s00018-011-0689-3 Accessed December 30th, 2021.
34. Lasser C, Jang SC, Lotvall J. Subpopulations of extracellular vesicles and their therapeutic potential. Mol Aspects Med. 2018 Apr;60:1-14. DOI: https://doi.org/10.1016/j.mam.2018.02.002 Accessed December 30th, 2021.
35. Malda J, Boere J, Van de Lest CH, *et al*. extracellular vesicles-new tool for joint repair and regeneration. Nat Rev Rheumatol. 2016;12(4):243-9. DOI: https://doi.org/10.1038/nrrheum.2015.170 Accessed December 30th, 2021.
36. D'Arrigo D, Roffi A, Cucchiarini M, *et al*. Secretome and extracellular vesicles as new biological therapies for knee osteoarthritis: A systematic review. J Clin Med. 2019;8(11):1867. Doi: https://doi.org/10.3390/jcm8111867 Accessed December 30th, 2021.
37. Wu J, Kuang L, Chen C, *et al*. miR-100-5p-abundant exosomes derived from infrapatellar fat pad MSCs protect articular cartilage and ameliorate gait abnormalities via inhibition of mTOP in osteoarthritis. Biomaterials. 2019;206:87-100. https://doi.org/10.1016/j.biomaterials.2019.03.022 Accessed December 30th, 2021.
38. Khatab S, Van Osch GJ, Kops N, *et al*. Mesenchymal stem cells secretomes reduces pain and prevents cartilage damage in a murine osteoarthritis model. Eur Cell Mater. 2018;36:218-30. https://doi.org/10.22203/eCM.v036a16 Accessed December 30th, 2021.
39. Fosset E, Khan WS, Longo UG, Smitham PJ. Effect of age and gender on cell proliferation and cell surface characterization of synovial fat pad derived mesenchymal stem cells. J Orthop Res. 2012 Jul;30(7):1013-8. https://doi.org/10.1002/jor.22057. Accessed December 31, 2021.
40. Khan WS, Adesida AB, Hardingham T. Hypoxic conditions increase hypoxia-inducible transcription factor 2alpha and enhance chondrogenesis in stem cells from the infrapatellar fat pad of osteoarthritis patients. Arthritis Res Ther. 2007;9(3):R55. https://doi.org/10.1186/ar2211
41. Davies BM, Rikabi S, French A, Pinedo-Villanueva R, Morrey ME, Wartolowska K, *et al*. Quantitative assessment of barriers to the clinical development and adoption of cellular therapies: a pilot study. J Tissue Enj. 2014 Sep 19;5:2041731414551764. https://doi.org/10.1177/2041731414551764. Accessed December 30th, 2021.
42. Moher D, Liberati A, Tetslaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. 2009;151:264-29, W64. https://doi.org/10.7326/0003-4819-151-200908180-00135 Accessed December 31, 2021.
43. Obremskey WT, Pappas N, Attallah-Wasif E, Tornetta P, Bhandari M. Level of evidence in orthopedic journals. J Bone Joint Surg. Am. 2005;87:2632-2638. https://doi.org/10.2106/jbjs.e.00370 Accessed December 31, 2021.
44. Coleman BD, Khan KM, Maffulli N, Cook JL, Wark JD. Studies on surgical outcome after patellar tendinopathy: clinical significance of methodological deficinetcies and guidelines for future studies. Victorian Institute of Sport tendon Study Group. Scand J Med Sci Sports. 2000;10:2-11 [PMB:10693606] Accessed December 31, 2021.
45. Shaikh N, Seah MKT and Khan WS. Systematic review on the use of autologous matrix-induced chondrogenesis for the repair of articular cartilage defects in patients. World J Orthop. 2017 Jul;8(7):588-601. https://doi.org/10.5312/wjo.v8.i7.588 Accessed December 31, 2021.
46. Reiner AT, Witwer KW, Van Balkom BWM, *et al*. concise review: developing best-practice models for the therapeutic use of extracellular vesicles. Stem Cells Transl Med. 2017;6(8):1730-9. DOI: https://doi.org/10.1002/sctm.17-0055 Accessed December 30th, 2021.