



## Stem-cell Therapy in Human Osteoarthritis: A Debate

Elaheh Ziaei Ziabari<sup>1,2</sup>, Alireza Ebrahimi<sup>3,\*</sup>, Soheil Ashkani-Esfahani<sup>4</sup> and Mohammad Razi<sup>5</sup>

<sup>1</sup>Rothman Institute, Thomas Jefferson University, Philadelphia, USA

<sup>2</sup>School of Mechanical Engineering, Iran University of Science and Technology, Tehran, Iran

<sup>3</sup>Student Research Committee, Shiraz University of Medical Sciences, Shiraz, Iran

<sup>4</sup>Department of Orthopaedic Surgery, Massachusetts General Hospital, Harvard Medical School, Boston, MA

<sup>5</sup>Department of Orthopaedic Surgery, Iran University of Medical Sciences (IUMS), Tehran, Iran

\*Corresponding author: Student Research Committee, Shiraz University of Medical Sciences, Shiraz, Iran. Email: alireza.ibrahim92@gmail.com

Received 2020 January 25; Accepted 2020 January 28.

Keywords: Osteoarthritis, Stem-Cell, Therapy

### Dear Editor,

Osteoarthritis (OA) is believed to be the most common joint disease worldwide with an estimated prevalence of knee and hip OA as 3.8% and 0.8%, respectively (1). The etiology of the disorders lies in the intrinsic joint and extrinsic environmental dynamics such as raised inflammatory cytokines, age, gender, genetics, weight, and injury (1). Treatment of OA mostly consists of conservative therapies that minimally modify the underlying deformities. In the severe cases of OA, total joint replacement has been suggested by OA Research Society International (2). Current investigations recommended less invasive procedures, such as intra-articular administration of hyaluronic acid, platelet-rich plasma, and anabolic cartilaginous bioreactors (3).

Stem-cell (SC) therapies are promptly becoming a possible approach towards the treatment of various diseases, as SCs could repair and regenerate several damaged tissues when exposed to proper cell differentiation mediators (4). In the past two decades, the administration of autologous and allogenic SCs has been practiced for the management of several musculoskeletal disorders and showed promising results (5). Mesenchymal stem cells (MSCs) have been increasingly used -via intra-articular injection- to improve hip and knee OA (5). In 2014, a proof-of-concept trial asserted that intra-articular administration of MSCs can improve knee OA by reviving the joint's function and pain (6). According to the present literature, the adverse effects of intra-articular injection of MSCs are negligible (5). These adverse effects may include post-procedural pain and swelling, which was mild and transient in previous investigations. However, it has been noted among 844 patients who received the therapy, two individuals displayed

serious complications related to the procedure, one pulmonary embolism and one infection at the bone marrow aspiration site (5).

In contrast to this auspicious evidence, total joint replacement is continued as the final treatment of end-stage OA. Artificial prostheses that are used for joint replacements have to be substituted after a few years, besides they lack the functions of normal joints (7); consequently, they could not satisfy the demands of younger and more active patients. Novel therapeutic approaches must be introduced and translated into clinics in order to provide these demands. Regarding SC therapies, researchers must explain the effects of age and systemic diseases on SCs, and the possible effects of joint inflammatory cytokines on SCs must be clarified as well (8). Moreover, the cartilaginous differentiation of SCs must be maintained over a long period, as SCs may be disproportionally converted to collagens if the environment is not appropriate (8). Providing better techniques for improving the mechanical integrity of the tissues and enhancing cartilage-to-cartilage and cartilage-to-bone integrations (among the SC derived and OA joint tissues) are among the main goals of recent research projects (8).

Extensive investigations suggest that SC therapy could be considered as a promising treatment of OA. MSCs have been introduced as a potential source for regenerative cellular therapies in the case of musculoskeletal diseases. Furthermore, previous level III/IV studies reported intra-articular injection of MSCs can improve osteoarthritis by increasing joint functions and reducing pain (9, 10). This therapeutic approach for patients with osteoarthritic joints may prevent or delay a total joint replacement, although there are serious barriers. Forthcoming studies

should be continued to solve these problems in order to create a reliable protocol for using SC therapy in patients suffering from OA.

### Footnotes

**Conflict of Interests:** None.

**Funding/Support:** Not declared.

### References

- Jevotovsky DS, Alfonso AR, Einhorn TA, Chiu ES. Osteoarthritis and stem cell therapy in humans: A systematic review. *Osteoarthritis Cartilage*. 2018;**26**(6):711–29. doi: [10.1016/j.joca.2018.02.906](https://doi.org/10.1016/j.joca.2018.02.906). [PubMed: [29544858](https://pubmed.ncbi.nlm.nih.gov/29544858/)].
- Zhang W, Nuki G, Moskowitz RW, Abramson S, Altman RD, Arden NK, et al. OARSIS recommendations for the management of hip and knee osteoarthritis: part III: Changes in evidence following systematic cumulative update of research published through January 2009. *Osteoarthritis Cartilage*. 2010;**18**(4):476–99. doi: [10.1016/j.joca.2010.01.013](https://doi.org/10.1016/j.joca.2010.01.013). [PubMed: [20170770](https://pubmed.ncbi.nlm.nih.gov/20170770/)].
- Patel S, Dhillon MS, Aggarwal S, Marwaha N, Jain A. Treatment with platelet-rich plasma is more effective than placebo for knee osteoarthritis: A prospective, double-blind, randomized trial. *Am J Sports Med*. 2013;**41**(2):356–64. doi: [10.1177/0363546512471299](https://doi.org/10.1177/0363546512471299). [PubMed: [23299850](https://pubmed.ncbi.nlm.nih.gov/23299850/)].
- Nadig RR. Stem cell therapy - Hype or hope? A review. *J Conserv Dent*. 2009;**12**(4):131–8. doi: [10.4103/0972-0707.58329](https://doi.org/10.4103/0972-0707.58329). [PubMed: [20543921](https://pubmed.ncbi.nlm.nih.gov/20543921/)]. [PubMed Central: [PMC2879724](https://pubmed.ncbi.nlm.nih.gov/PMC2879724/)].
- Peeters CM, Leijns MJ, Reijman M, van Osch GJ, Bos PK. Safety of intra-articular cell-therapy with culture-expanded stem cells in humans: A systematic literature review. *Osteoarthritis Cartilage*. 2013;**21**(10):1465–73. doi: [10.1016/j.joca.2013.06.025](https://doi.org/10.1016/j.joca.2013.06.025). [PubMed: [23831631](https://pubmed.ncbi.nlm.nih.gov/23831631/)].
- Jo CH, Lee YG, Shin WH, Kim H, Chai JW, Jeong EC, et al. Intra-articular injection of mesenchymal stem cells for the treatment of osteoarthritis of the knee: A proof-of-concept clinical trial. *Stem Cells*. 2014;**32**(5):1254–66. doi: [10.1002/stem.1634](https://doi.org/10.1002/stem.1634). [PubMed: [24449146](https://pubmed.ncbi.nlm.nih.gov/24449146/)].
- Kurtz S, Ong K, Lau E, Mowat F, Halpern M. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. *J Bone Joint Surg Am*. 2007;**89**(4):780–5. doi: [10.2106/JBJS.F.00222](https://doi.org/10.2106/JBJS.F.00222). [PubMed: [17403800](https://pubmed.ncbi.nlm.nih.gov/17403800/)].
- Diekmann BO, Guilak F. Stem cell-based therapies for osteoarthritis: Challenges and opportunities. *Curr Opin Rheumatol*. 2013;**25**(1):19–26. doi: [10.1097/BOR.0b013e32835aa28d](https://doi.org/10.1097/BOR.0b013e32835aa28d). [PubMed: [23190869](https://pubmed.ncbi.nlm.nih.gov/23190869/)]. [PubMed Central: [PMC3616879](https://pubmed.ncbi.nlm.nih.gov/PMC3616879/)].
- Koh YG, Jo SB, Kwon OR, Suh DS, Lee SW, Park SH, et al. Mesenchymal stem cell injections improve symptoms of knee osteoarthritis. *Arthroscopy*. 2013;**29**(4):748–55. doi: [10.1016/j.arthro.2012.11.017](https://doi.org/10.1016/j.arthro.2012.11.017). [PubMed: [23375182](https://pubmed.ncbi.nlm.nih.gov/23375182/)].
- Pas HI, Winters M, Haisma HJ, Koenis MJ, Tol JL, Moen MH. Stem cell injections in knee osteoarthritis: A systematic review of the literature. *Br J Sports Med*. 2017;**51**(15):1125–33. doi: [10.1136/bjsports-2016-096793](https://doi.org/10.1136/bjsports-2016-096793). [PubMed: [28258177](https://pubmed.ncbi.nlm.nih.gov/28258177/)].