



TITLE: Autologous Mesenchymal Stem Cell Therapy for Orthopedic Patients: Clinical Effectiveness

DATE: 10 November 2015

RESEARCH QUESTION

What is the clinical effectiveness of autologous mesenchymal stem cell therapy for adult orthopedic patients?

KEY FINDINGS

One systematic review, two randomized controlled trials, and four non-randomized studies were identified regarding the clinical effectiveness of autologous mesenchymal stem cell therapy for adult orthopedic patients.

METHODS

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and non-randomized studies. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2010 and October 28, 2015. Internet links were provided, where available.

The summary of findings was prepared from the abstracts of the relevant information. Please note that data contained in abstracts may not always be an accurate reflection of the data contained within the full article.

SELECTION CRITERIA

One reviewer screened citations and selected studies based on the inclusion criteria presented in Table 1.

Disclaimer: The Rapid Response Service is an information service for those involved in planning and providing health care in Canada. Rapid responses are based on a limited literature search and are not comprehensive, systematic reviews. The intent is to provide a list of sources of the best evidence on the topic that CADTH could identify using all reasonable efforts within the time allowed. Rapid responses should be considered along with other types of information and health care considerations. The information included in this response is not intended to replace professional medical advice, nor should it be construed as a recommendation for or against the use of a particular health technology. Readers are also cautioned that a lack of good quality evidence does not necessarily mean a lack of effectiveness particularly in the case of new and emerging health technologies, for which little information can be found, but which may in future prove to be effective. While CADTH has taken care in the preparation of the report to ensure that its contents are accurate, complete and up to date, CADTH does not make any guarantee to that effect. CADTH is not liable for any loss or damages resulting from use of the information in the report.

Copyright: This report contains CADTH copyright material and may contain material in which a third party owns copyright. **This report may be used for the purposes of research or private study only.** It may not be copied, posted on a web site, redistributed by email or stored on an electronic system without the prior written permission of CADTH or applicable copyright owner.

Links: This report may contain links to other information available on the websites of third parties on the Internet. CADTH does not have control over the content of such sites. Use of third party sites is governed by the owners' own terms and conditions.

Table 1: Selection Criteria

Population	Adult orthopedic patients
Intervention	Autologous mesenchymal stem cell therapy including, but not limited to: adipose derived stem/stromal cells (ADSC) and bone marrow aspirate concentrate (BMAC) alone or in combination
Comparator	Relevant comparator (e.g., bone graft, pain management, surgery)
Outcomes	Clinical effectiveness (e.g., pain reduction, functional measures, improved range of motion, quality of life); Safety (e.g., tolerability of aspiration procedure)
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies

RESULTS

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials, and non-randomized studies.

One systematic review, two randomized controlled trials, and four non-randomized studies were identified regarding the clinical effectiveness of autologous mesenchymal stem cell therapy for adult orthopedic patients. No relevant health technology assessments were identified.

Additional references of potential interest are provided in the appendix.

OVERALL SUMMARY OF FINDINGS

One systematic review¹ examined the adverse events related to intra-articular treatment of osteoarthritis and cartilage repair with autologous bone marrow-derived mesenchymal stem cells (MSCs). Four serious adverse events and 22 possibly related adverse events were reported in 844 procedures. The most reported adverse events were an increase in pain and swelling and dehydration following the bone marrow aspiration procedure.

One randomized controlled trial² (RCT) compared the outcomes of matrix-induced autologous mesenchymal stem cell implantation versus matrix-induced autologous chondrocyte implantation in the treatment of chondral defects of the knee. A significant improvement was observed in both groups at 24 months following the procedure. The group that received matrix-induced autologous mesenchymal stem cell implantation had significantly better functional, pain, and quality of life outcomes at follow-up.

One RCT³ examined the use of intra-articular cultured autologous bone marrow-derived MSC injections plus microfracture and medial opening-wedge high tibial osteotomy compared with a control group. Following the procedure, symptom and functional scale scores were significantly better in the treatment group.

One non-randomized study⁴ compared the outcome of matrix-induced autologous chondrocyte implantation and bone marrow aspirate concentrate-derived multipotent stem cell implantation in patellofemoral chondral lesions. Symptom and functional scale scores were significantly improved in both groups, but there was not a significant difference in outcomes between groups. No adverse reactions or infections were identified. In another study, patients with osteoarthritis of the knee underwent surgical debridement and infrapatellar fat pad-derived mesenchymal

stem cell injection and were compared with a control group.⁵ Symptom and functional scale scores were significantly improved in the treatment group; however, clinical outcomes were not significantly different between groups. No major adverse events were reported.

One non-randomized study⁶ compared a novel minimally invasive approach to cartilage repair with MSCs with an open surgical technique. Significant improvement in scale scores was reported in both groups following the procedures. No adverse events were reported in either group. One non-randomized study⁷ evaluated first-generation autologous chondrocyte implantation versus autologous bone marrow-derived MSCs for cartilage repair. Symptom and functional scale scores were significantly improved in both groups and clinical outcomes were not significantly different between groups.

REFERENCES SUMMARIZED

Health Technology Assessments

No literature identified.

Systematic Reviews and Meta-analyses

1. Peeters CM, Leijs 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 Oct;21(10):1465-73.
[PubMed: PM23831631](#)

Randomized Controlled Trials

2. Akgun I, Unlu MC, Erdal OA, Ogut T, Erturk M, Ovali E, et al. Matrix-induced autologous mesenchymal stem cell implantation versus matrix-induced autologous chondrocyte implantation in the treatment of chondral defects of the knee: a 2-year randomized study. *Arch Orthop Trauma Surg*. 2015 Feb;135(2):251-63.
[PubMed: PM25548122](#)
3. Wong KL, Lee KB, Tai BC, Law P, Lee EH, Hui JH. Injectable cultured bone marrow-derived mesenchymal stem cells in varus knees with cartilage defects undergoing high tibial osteotomy: a prospective, randomized controlled clinical trial with 2 years' follow-up. *Arthroscopy*. 2013 Dec;29(12):2020-8.
[PubMed: PM24286801](#)

Non-Randomized Studies

4. Gobbi A, Chaurasia S, Karnatzikos G, Nakamura N. Matrix-induced autologous chondrocyte implantation versus multipotent stem cells for the treatment of large patellofemoral chondral lesions: a nonrandomized prospective trial. *Cartilage*. 2015 Apr;6(2):82-97.
[PubMed: PM26069711](#)
5. Koh YG, Choi YJ. Infrapatellar fat pad-derived mesenchymal stem cell therapy for knee osteoarthritis. *Knee*. 2012 Dec;19(6):902-7.
[PubMed: PM22583627](#)
6. Lee KB, Wang VT, Chan YH, Hui JH. A novel, minimally-invasive technique of cartilage repair in the human knee using arthroscopic microfracture and injections of mesenchymal stem cells and hyaluronic acid--a prospective comparative study on safety and short-term efficacy. *Ann Acad Med Singapore*. 2012 Nov;41(11):511-7.
[PubMed: PM23235728](#)
7. Nejadnik H, Hui JH, Feng Choong EP, Tai BC, Lee EH. Autologous bone marrow-derived mesenchymal stem cells versus autologous chondrocyte implantation: an observational cohort study. *Am J Sports Med*. 2010 Jun;38(6):1110-6.
[PubMed: PM20392971](#)

PREPARED BY:

Canadian Agency for Drugs and Technologies in Health

Tel: 1-866-898-8439

www.cadth.ca

APPENDIX – FURTHER INFORMATION:**Systematic Reviews and Meta-Analyses – Origin of Stem Cells Not Specified in Abstract**

8. Oehme D, Goldschlager T, Ghosh P, Rosenfeld JV, Jenkin G. Cell-based therapies used to treat lumbar degenerative disc disease: a systematic review of animal studies and human clinical trials. *Stem Cells Int* [Internet]. 2015 [cited 2015 Nov 10];2015:946031. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4446495>
[PubMed: PM26074979](#)
9. Perdisa F, Gostynska N, Roffi A, Filardo G, Marcacci M, Kon E. Adipose-derived mesenchymal stem cells for the treatment of articular cartilage: a systematic review on preclinical and clinical evidence. *Stem Cells Int* [Internet]. 2015 [cited 2015 Nov 10];2015:597652. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4512635>
[PubMed: PM26240572](#)
10. Xia P, Wang X, Lin Q, Li X. Efficacy of mesenchymal stem cells injection for the management of knee osteoarthritis: a systematic review and meta-analysis. *Int Orthop*. 2015 May 6. [Epub ahead of print]
[PubMed: PM25944079](#)
11. Xu S, Liu H, Xie Y, Sang L, Liu J, Chen B. Effect of mesenchymal stromal cells for articular cartilage degeneration treatment: a meta-analysis. *Cytotherapy*. 2015 Oct;17(10):1342-52.
[PubMed: PM26122717](#)
12. Gopal K, Amirhamed HA, Kamarul T. Advances of human bone marrow-derived mesenchymal stem cells in the treatment of cartilage defects: a systematic review. *Exp Biol Med (Maywood)*. 2014 Jun;239(6):663-9.
[PubMed: PM24764239](#)
13. Li X, Xu X, Wu W. Comparison of bone marrow mesenchymal stem cells and core decompression in treatment of osteonecrosis of the femoral head: a meta-analysis. *Int J Clin Exp Pathol* [Internet]. 2014 [cited 2015 Nov 10];7(8):5024-30. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4152064>
[PubMed: PM25197374](#)
14. Filardo G, Madry H, Jelic M, Roffi A, Cucchiari M, Kon E. Mesenchymal stem cells for the treatment of cartilage lesions: from preclinical findings to clinical application in orthopaedics. *Knee Surg Sports Traumatol Arthrosc*. 2013 Aug;21(8):1717-29.
[PubMed: PM23306713](#)

Non-Randomized Studies*No Comparator Group*

15. Centeno CJ, Al-Sayegh H, Bashir J, Goodyear S, Freeman MD. A prospective multi-site registry study of a specific protocol of autologous bone marrow concentrate for the treatment of shoulder rotator cuff tears and osteoarthritis. *J Pain Res* [Internet]. 2015 [cited 2015 Nov 10];8:269-76. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4463777>
[PubMed: PM26089699](#)
16. Gross JB, Diligent J, Bensoussan D, Galois L, Stoltz JF, Mainard D. Percutaneous autologous bone marrow injection for treatment of delayed and non-union of long bone: a retrospective study of 45 cases. *Biomed Mater Eng*. 2015;25(1 Suppl):187-97.
[PubMed: PM25538069](#)
17. Koh YG, Choi YJ, Kwon SK, Kim YS, Yeo JE. Clinical results and second-look arthroscopic findings after treatment with adipose-derived stem cells for knee osteoarthritis. *Knee Surg Sports Traumatol Arthrosc*. 2015 May;23(5):1308-16.
[PubMed: PM24326779](#)
18. Mochida J, Sakai D, Nakamura Y, Watanabe T, Yamamoto Y, Kato S. Intervertebral disc repair with activated nucleus pulposus cell transplantation: a three-year, prospective clinical study of its safety. *Eur Cell Mater*. 2015;29:202-12.
[PubMed: PM25794529](#)
19. Pettine KA, Murphy MB, Suzuki RK, Sand TT. Percutaneous injection of autologous bone marrow concentrate cells significantly reduces lumbar discogenic pain through 12 months. *Stem Cells*. 2015 Jan;33(1):146-56.
[PubMed: PM25187512](#)
20. Aoyama T, Goto K, Kakinoki R, Ikeguchi R, Ueda M, Kasai Y, et al. An exploratory clinical trial for idiopathic osteonecrosis of femoral head by cultured autologous multipotent mesenchymal stromal cells augmented with vascularized bone grafts. *Tissue Eng Part B Rev* [Internet]. 2014 Aug [cited 2015 Nov 10];20(4):233-42. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4123560>
[PubMed: PM24593258](#)
21. Cai J, Wu Z, Huang L, Chen J, Wu C, Wang S, et al. Cotransplantation of bone marrow mononuclear cells and umbilical cord mesenchymal stem cells in avascular necrosis of the femoral head. *Transplant Proc*. 2014 Jan;46(1):151-5.
[PubMed: PM24507042](#)
22. Calori GM, Mazza E, Colombo M, Mazzola S, Mineo GV, Giannoudis PV. Treatment of AVN using the induction chamber technique and a biological-based approach: indications and clinical results. *Injury*. 2014 Feb;45(2):369-73.
[PubMed: PM24119830](#)

23. Buda R, Vannini F, Cavallo M, Baldassarri M, Luciani D, Mazzotti A, et al. One-step arthroscopic technique for the treatment of osteochondral lesions of the knee with bone-marrow-derived cells: three years results. *Musculoskelet Surg*. 2013 Aug;97(2):145-51. [PubMed: PM23420394](#)
24. 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 Apr;29(4):748-55. [PubMed: PM23375182](#)
25. Mao Q, Jin H, Liao F, Xiao L, Chen D, Tong P. The efficacy of targeted intraarterial delivery of concentrated autologous bone marrow containing mononuclear cells in the treatment of osteonecrosis of the femoral head: a five year follow-up study. *Bone* [Internet]. 2013 Dec [cited 2015 Nov 10];57(2):509-16. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3927161> [PubMed: PM23994171](#)
26. Orozco L, Munar A, Soler R, Alberca M, Soler F, Huguet M, et al. Treatment of knee osteoarthritis with autologous mesenchymal stem cells: a pilot study. *Transplantation*. 2013 Jun 27;95(12):1535-41. [PubMed: PM23680930](#)
27. Pak J, Chang JJ, Lee JH, Lee SH. Safety reporting on implantation of autologous adipose tissue-derived stem cells with platelet-rich plasma into human articular joints. *BMC Musculoskelet Disord* [Internet]. 2013 [cited 2015 Nov 10];14:337. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4219585> [PubMed: PM24289766](#)
28. Pak J, Lee JH, Lee SH. A novel biological approach to treat chondromalacia patellae. *PLoS ONE* [Internet]. 2013 [cited 2015 Nov 10];8(5):e64569. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3659098> [PubMed: PM23700485](#)
29. Skowronski J, Skowronski R, Rutka M. Cartilage lesions of the knee treated with blood mesenchymal stem cells - results. *Ortop Traumatol Rehabil*. 2012 Nov;14(6):569-77. [PubMed: PM23382284](#)
30. Orozco L, Soler R, Morera C, Alberca M, Sanchez A, Garcia-Sancho J. Intervertebral disc repair by autologous mesenchymal bone marrow cells: a pilot study. *Transplantation*. 2011 Oct 15;92(7):822-8. [PubMed: PM21792091](#)

Comparative Studies – Origin of Stem Cells Not Specified in Abstract

31. Koh YG, Kwon OR, Kim YS, Choi YJ. Comparative outcomes of open-wedge high tibial osteotomy with platelet-rich plasma alone or in combination with mesenchymal stem cell treatment: a prospective study. *Arthroscopy*. 2014 Nov;30(11):1453-60. [PubMed: PM25108907](#)

32. Kim YS, Park EH, Kim YC, Koh YG. Clinical outcomes of mesenchymal stem cell injection with arthroscopic treatment in older patients with osteochondral lesions of the talus. *Am J Sports Med.* 2013 May;41(5):1090-9.

[PubMed: PM23460335](#)

Review Articles

33. Counsel PD, Bates D, Boyd R, Connell DA. Cell therapy in joint disorders. *Sports Health.* 2015 Jan;7(1):27-37.

[PubMed: PM25553210](#)

34. Papakostidis C, Tosounidis TH, Jones E, Giannoudis PV. The role of "cell therapy" in osteonecrosis of the femoral head. *Acta Orthop.* 2015 Jul 29;1-7. [Epub ahead of print]

[PubMed: PM26220203](#)

35. Vonk LA, de Windt TS, Slaper-Cortenbach IC, Saris DB. Autologous, allogeneic, induced pluripotent stem cell or a combination stem cell therapy? Where are we headed in cartilage repair and why: a concise review. *Stem Cell Res Ther* [Internet]. 2015 [cited 2015 Nov 10];6:94. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4430904>

[PubMed: PM25976213](#)

36. Wolfstadt JI, Cole BJ, Ogilvie-Harris DJ, Viswanathan S, Chahal J. Current concepts: the role of mesenchymal stem cells in the management of knee osteoarthritis. *Sports Health.* 2015 Jan;7(1):38-44.

[PubMed: PM25553211](#)

37. Health Policy Advisory Committee on Technology. New and emerging orthopaedic technologies in the Australian and New Zealand public health services [Internet]. Brisbane: HealthPACT Secretariat; 2014 Nov [cited 2015 Nov 10]. (New and emerging health technology report). Available from:

<https://www.health.qld.gov.au/healthpact/docs/nehtr/nehtr-november2014.pdf>

See: *Stem cells in orthopaedics*

38. Rodriguez-Merchan EC. Intra-articular injections of mesenchymal stem cells for knee osteoarthritis. *Am J Orthop (Belle Mead NJ).* 2014 Dec;43(12):E282-E291.

[PubMed: PM25490014](#)

39. NIHR Horizon Scanning Centre. Regenerative medicine in the management of musculoskeletal disorders [Internet]. Birmingham (UK): University of Birmingham; 2013 Jan [cited 2015 Nov 10]. Available from: <http://www.hsrhc.nihr.ac.uk/topics/regenerative-medicine-in-the-management-of-musculoskeletal-disorders-review/>