STEM CELLS AND BIOTECHNOLOGY CENTER

ISSN: 3100-9506

EVIDENCE OF THE MEDICAL BENEFITS OF STEM CELLS

Regencord

N° 4 APRIL 2025

The magazine **"Evidence of the medical benefits of stem cells"**
is a biennial publication of the Stem Cells and Biotechnology Center (Regencord)

No. 4 April 2025
Pereira, Colombia

Editor
Stem Cells and Biotechnology Center, Regencord.
www.regencord.com
gerencia@regencord.com

Author
Carlos Alberto Isaza Mejía
Medical Pharmacologist PhD HC
Regencord Scientific Director
Email: caisaza@regencord.com

Publishers
Grafitel y Cia S en C (Pereira)
ISSN: 3100-9506

CONTENTS

INTRODUCTION

> ***"The regenerative medicine revolution is upon us. Like iron and steel to the industrial revolution, like the microchip to the tech revolution, stem cells will be the driving force of this next revolution."***

Cade Hildreth, founder of BioInformant, a stem cell industry research firm. Citado por: Tony Robbins, Peter Diamandis and Robert Hariri. Life Force; Simon and Schuster, 2022.

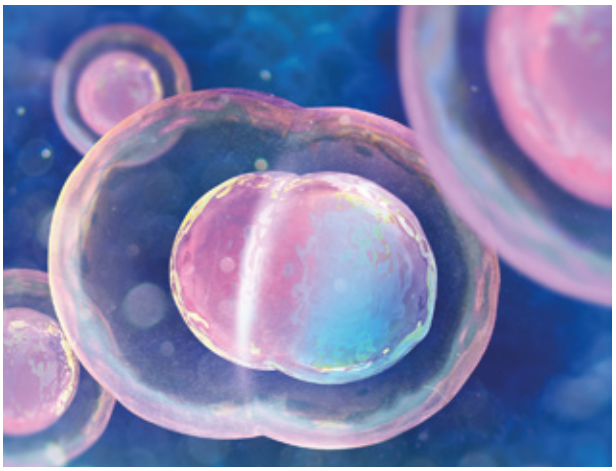
> ***"Stem cells seem to hold major promise for contemporary medicine, one which could almost be more significant than a discovery of DNA".***

Kurpisz M. New Technologies Based on Stem Cell-Therapies in Regenerative Medicine and Reproductive Biology. Cells. 2022;12(1):95.

> ***"Regenerative medicine is the new frontier of medicine"***

Lampiasi N. Mesenchymal Stem Cells: What We Have Learned and How to Manage Them. Biology (Basel). 2024;14(1):1.

Stem cells are present in all tissues of the body, where they remain in a quiescent and undifferentiated state within specific locations known as "stem cell niches." Despite their dormant state, they retain full capacity to generate progeny in response to the body's needs. They exhibit distinctive properties that endow them with remarkable therapeutic potential. First, they can proliferate indefinitely while maintaining their stem cell status (symmetric cell division). Second, under appropriate stimuli, they can differentiate into various specialized cells, such as those of the brain, heart, liver, and others (asymmetric cell division). Third, they are capable of targeted migration throughout the body in response to biochemical signals emitted by damaged or diseased tissues. Thus, they remain with us throughout life, although they progressively lose vitality as we age or develop disease.



The main breakthrough in the development of "regenerative medicine" was the ability to isolate stem cells from an individual, culture and expand them *in vitro*, and then transfer them either back to the original donor (autologous transplantation) or to another person (allogeneic transplantation), thereby harnessing their therapeutic potential. Thus, it enabled the large-scale production and availability of stem cells in quantities sufficient for various applications in which their usefulness has been demonstrated.

Autologous stem cells are being used less frequently for therapeutic purposes, not only because a patient's underlying disease may impair their own cells, but also because stem cells age alongside the individual. It has been shown that as stem cells grow older, they may acquire anti-regenerative properties (for instance, promoting cell death). On the other hand, among exogenous sources of stem cells, those derived from the wall of the umbilical cord stand out as an excellent source of "universal donor" cells. These cells do not trigger immune rejection, exhibit high

proliferative capacity, possess broad differentiation potential, retain their biological properties over time, and can be obtained in large quantities from non-invasive sources, without the ethical and legal concerns associated with other sources. Finally, these cells can be cryopreserved and stored under laboratory conditions for extended periods without compromising their identity (surface marker and epigenetic profile), their proliferation and differentiation capacity, or their therapeutic potential.

HOW DO STEM CELLS WORK?

These cells exert their therapeutic effects through four primary mechanisms:

1. Stem cells can differentiate into the specific cell types of the affected organ, thereby replacing injured or dead native cells.

2. Through direct cell-to-cell interaction, stem cells transfer intracellular organelles to local cells that are undergoing aging and cell death. Such is the case of mitochondrial transfer, organelles with vital roles in energy production, regeneration, and cellular aging, through which native diseased cells are revitalized and biological balance is restored.

3. Stem cells also engage in direct cell-to-cell communication by transferring transcription factors that carry epigenetic instructions, prompting surrounding cells to modify their harmful behavior, for example, inducing pro-inflammatory white blood cells to shift toward an anti-inflammatory phenotype.

4. Once they reach the affected organ, stem cells can release hundreds of biologically active molecules that help counteract damage (such as inflammation, oxidative stress, fibrosis, or cell death).

Finally, as science and technology advance continuously, it is relevant to mention the stem cell-derived extracellular vesicles (EVs), which are loaded with biologically active molecules and, according to current scientific evidence, have practically all the therapeutic virtues of these cells, but with important advantages, such as their small size that allows them to easily reach the injured area and to escape destruction by the immune system; not inducing an immune response in the patient, have no tumorigenic activity (tumor formation), as they are not living organisms that self-replicate and, finally, be stable particles easily modifiable and storable for long periods. For these reasons, many authors consider EV-based therapy to represent the “second generation” of regenerative medicine.

The wide safety margin and promising potential of stem cells and EVs suggest that we are on the verge of a new therapeutic paradigm. However, it must be acknowledged that, in many cases, clinical evidence remains limited, and several challenges must be overcome before stem cells can be incorporated into official treatment protocols. It is also important to clarify that this publication does not aim to provide an exhaustive review of the available evidence on the clinical uses of stem cells. Instead, it briefly highlights those clinical conditions for which there is an acceptable level of evidence regarding the safety and efficacy of stem cells/EVs, supported by high-quality scientific literature.

Stem Cells and Biotechnology Center
-Regencord-

OSTEOARTICULAR DISEASE AND PAIN

Osteoarticular disorders, including osteoarthritis, spinal degenerative conditions and, tendon injuries, are among the most extensively studied in regenerative medicine. This field is now recognized as a safe and cost-effective approach with the potential to repair damage and promote tissue regeneration (1).

OSTEOARTHRITIS

Articular cartilage has a low concentration of stem cells and poor vascularization, which explains its limited self-repair potential. Stem cells repair articular cartilage and restore joint function through several mechanisms: a) differentiating into new chondrocytes (the normal cartilage cells); b) regulating inflammation in the joint microenvironment; and c) alleviating pain (2,3).

Conventional osteoarthritis treatment, which includes physical therapy, analgesics, and anti-inflammatory agents, provides only modest clinical benefits and carries a high incidence of adverse events from medications or surgical intervention. On the contrary, dozens of clinical studies and meta-analyses involving thousands of patients have demonstrated that intra-articular stem cell therapy leads to significant cartilage regeneration and improvement in clinical parameters (pain and functional limitation), imaging findings, arthroscopic outcomes, and quality of life (4-19). An increasing number of experts suggest that stem cells (or their exosomes) may exert a preventive effect on the progression of osteoarthritis and advise against considering surgery as the sole treatment option for elderly patients with severe osteoarthritis (20-22). This may be the most cost-effective treatment compared to options such as glucocorticoids or hyaluronic acid, particularly for

joints where stem cells can be applied locally (23-26). It is important to mention that the combination of stem cells with hyaluronic acid or platelet-rich plasma has an analgesic effect and achieves superior outcomes on the WOMAC scale compared to either treatment alone (27).

MUSCULOSKELETAL INJURIES

It has been demonstrated that stem cells and growth factors enhance the recovery of a wide range of musculoskeletal injuries, with fewer adverse effects compared to traditional approaches based on analgesics, anti-inflammatory drugs, physical therapy, and, when conservative management is insufficient, surgery. Frequently, when non-surgical treatment is unsatisfactory, glucocorticoid infiltration at the injury site is used. However, its effectiveness is temporary, and these drugs carry the risk of

gradually altering tissue metabolism, leading to weakening and an increased probability of injury progression. Regarding regenerative medicine, most published clinical studies indicate that the intralesional application of stem cells, with or without growth factors, improves pain, functional performance, and structural defects of the injured tissue. Among the musculoskeletal injuries that respond positively to regenerative therapy are plantar fasciitis, tendinopathies, musculotendinous tears, ligament injuries and ruptures, rotator cuff tears, arthritis, and avascular necrosis of the femoral head (28-33).

DEGENERATION OF THE INTERVERTEBRAL DISC

The intervertebral disc prevents direct contact between vertebrae and absorbs compressive forces on the spine. Intervertebral disc degeneration is associated with the loss of vitality in its stem cells, leading to disc deformation and instability. This process can result in localized pain or even severe, disabling nerve injury. Treatment options for disc degeneration include palliative approaches such as pain medication and physical therapy. In many cases, surgery is required, though it may lead to biomechanical complications and accelerated degeneration of adjacent segments. The intradiscal application of stem cells is a safe, minimally invasive procedure with long-lasting benefits. It does not require surgery or hospitalization and compares favorably to surgical interventions such as spinal fusion or disc replacement, offering similar outcomes at significantly lower costs (34-38).

SPINAL AND LOWER BACK PAIN

Aparte del disco, todas las demás estructuras que hacen parte de la anatomía de la columna (músculos, articulaciones intervertebrales, raíces nerviosas, articulaciones sacroilíacas, etc) son capaces de provocar dolor en la región comprometida o irradiado a la extremidad inferior. En estos casos el beneficio de la infiltración local de células madre/exosomas ya ha sido demostrado en ensayos clínicos controlados, con una relación riesgo/beneficio superior a otras alternativas convencionales (39-43).

PAIN

Clinical evidence is steadily accumulating, demonstrating the benefits of stem cells/exosomes in the treatment of neuropathic pain, including pain secondary to complete spinal cord injury or diabetic neuropathy. This suggests that stem cell therapy may represent a novel approach to treating a condition that significantly impairs patients' quality of life and for which conventional medicine offers limited treatment options (44). It has been demonstrated that, at injury sites, stem cells inhibit the production of pain-inducing substances while simultaneously releasing analgesic compounds, thereby correcting the imbalance between pain mediators and analgesic factors. This mechanism establishes stem cell therapy as a novel strategy for managing pain associated with a wide range of diseases (45-57). It is useful to note that some evidence suggests stem cells enhance the analgesic effect of opioids in cases of intractable cancer-related pain (58).

REFERENCES

1. Goulian AJ, Goldstein B, Saad MA. Advancements in Regenerative Therapies for Orthopedics: A Comprehensive Review of Platelet-Rich Plasma, Mesenchymal Stem Cells, Peptide Therapies, and Biomimetic Applications. J Clin Med. 2025;14(6):2061. doi: 10.3390/jcm14062061.
2. Tian R, Su S, Yu Y, Liang S, Ma C, Jiao Y, et al. Revolutionizing osteoarthritis treatment: How mesenchymal stem cells hold the key. Biomed Pharmacother. 2024;173:116458. doi: 10.1016/j.biopha.2024.116458.
3. Zou X, Xu H, Qian W. Macrophage Polarization in the Osteoarthritis Pathogenesis and Treatment. Orthop Surg. 2024. doi: 10.1111/os.14302.
4. Lin J, Huang J, Jiao Z, Nian M, Li C, Dai Y, et al. Mesenchymal stem cells for osteoarthritis: Recent advances in related cell therapy. Bioeng Transl Med. 2024;10(1):e10701. doi: 10.1002/btm2.10701.
5. Zhang X, Cui C, Lin F. Efficacy and safety of mesenchymal stem cell injections for knee osteoarthritis: A systematic review and meta-analysis. J Res Med Sci. 2024;29:55. doi: 10.4103/jrms.jrms_515_23.
6. Lee H, Lim Y, Lee SH. Rapid-acting pain relief in knee osteoarthritis: autologous-cultured adipose-derived mesenchymal stem cells outperform stromal vascular fraction: a systematic review and meta-analysis. Stem Cell Res Ther. 2024;15(1):446. doi: 10.1186/s13287-024-04034-2.
7. Perez OF, Warburton C, Philippon MC Jr, Philippon MJ, Best TM. The Efficacy of Bone Marrow Stem Cell Therapy in Hip Osteoarthritis: A Scoping Review. HSS J. 2024:15563316241259035. doi: 10.1177/15563316241259035.
8. Xiao Z, Wang X, Li C, Luo L, Li W. Effects of the umbilical cord mesenchymal stem cells in the treatment of knee osteoarthritis: A systematic review and meta-analysis. Medicine (Baltimore). 2024;103(46):e40490. doi: 10.1097/MD.0000000000040490.
9. Tabet CG, Pacheco RL, Martimbianco ALC, Riera R, Hernandez AJ, Bueno DF, Fernandes TL. Advanced therapy with mesenchymal stromal cells for knee osteoarthritis: Systematic review and meta-analysis of randomized controlled trials. J Orthop Translat. 2024;48:176-189. doi: 10.1016/j.jot.2024.07.012.
10. Vadhan A, Gupta T, Hsu WL. Mesenchymal Stem Cell-Derived Exosomes as a Treatment Option for Osteoarthritis. Int J Mol Sci. 2024;25(17):9149. doi: 10.3390/ijms25179149.
11. Giorgino R, Alessandri Bonetti M, Migliorini F, Nannini A, Vaienti L, et al. Management of hip osteoarthritis: harnessing the potential of mesenchymal stem cells-a

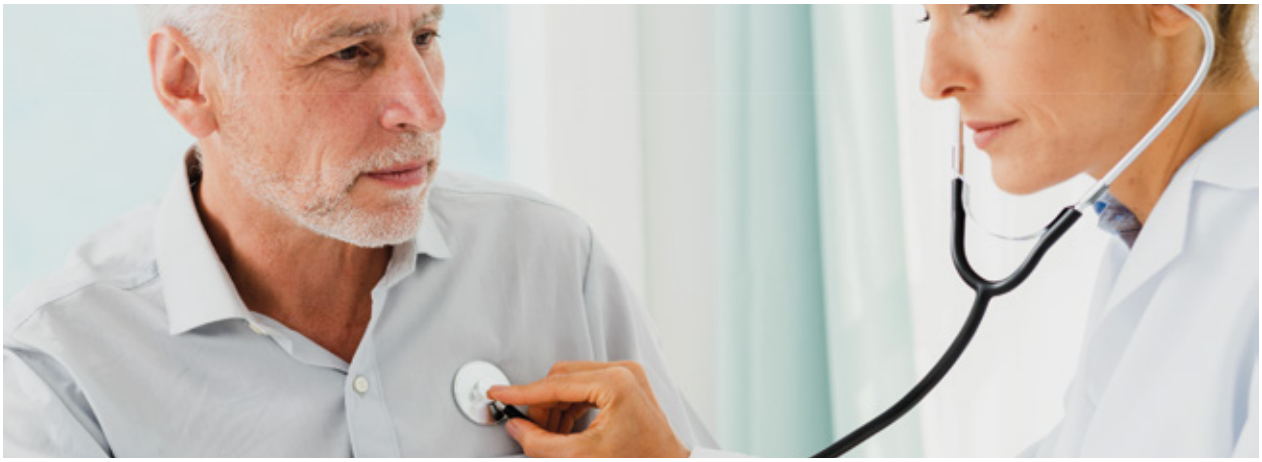
systematic review. Eur J Orthop Surg Traumatol. 2024. doi: 10.1007/s00590-024-04089-0.
12. Freitag J, Chamberlain M, Wickham J, Shah K, Cicuttini F, Wang Y, et al. Safety and efficacy of an allogeneic adipose-derived mesenchymal stem cell preparation in the treatment of knee osteoarthritis: A Phase I/IIa randomised controlled trial. Osteoarthr Cartil Open. 2024;6(3):100500. doi: 10.1016/j.ocarto.2024.100500.
13. Spasovski D, Spasovski V, Bascarevic Z, Stojiljkovic M, Andjelkovic M, Pavlovic S. Seven-Year Longitudinal Study: Clinical Evaluation of Knee Osteoarthritic Patients Treated with Mesenchymal Stem Cells. J Clin Med. 2024;13(13):3861. doi: 10.3390/jcm13133861.
14. Tian X, Qu Z, Cao Y, Zhang B. Relative efficacy and safety of mesenchymal stem cells for osteoarthritis: a systematic review and meta-analysis of randomized controlled trials. Front Endocrinol (Lausanne). 2024;15:1366297. doi: 10.3389/fendo.2024.1366297.
15. Ding QX, Wang X, Li TS, Li YF, Li WY, Gao JH, et al. Comparative Analysis of Short-Term and Long-Term Clinical Efficacy of Mesenchymal Stem Cells from Different Sources in Knee Osteoarthritis: A Network Meta-Analysis. Stem Cells Int. 2024;2024:2741681. doi: 10.1155/2024/2741681.
16. Epanomeritakis IE, Khan WS. Adipose-derived regenerative therapies for the treatment of knee osteoarthritis. World J Stem Cells. 2024;16(4):324-333. doi: 10.4252/wjsc.v16.i4.324.
17. Jung SH, Jung M, Chung K, Kim S, Park J, Hong J, et al. Prognostic Factors for Clinical Outcome and Cartilage Regeneration after Implantation of Allogeneic Human Umbilical Cord Blood-Derived Mesenchymal Stem Cells in Large-Sized Cartilage Defects with Osteoarthritis. Cartilage. 2024:19476035241231372. doi: 10.1177/19476035241231372.
18. Cao M, Ou Z, Sheng R, Wang Q, Chen X, Zhang C, et al. Efficacy and safety of mesenchymal stem cells in knee osteoarthritis: a systematic review and meta-analysis of randomized controlled trials. Stem Cell Res Ther. 2025;16(1):122. doi: 10.1186/s13287-025-04252-2.
19. Ishak-Samrin M, Naina-Mohamed I, Zulfarina MS, Abdul Wahid SF, Mohd Don AF, Mohamad N, et al. Treatment of Knee Osteoarthritis and Chondral Injury with Umbilical Cord/Wharton's Jelly-Derived Mesenchymal Stem Cells: A Systematic Review of Safety and Efficacy. J Funct Biomater. 2025;16(3):84. doi: 10.3390/jfb16030084.
20. Lee BW, Lee JJ, Jung JY, Ju JH. Intra-Articular Injection of Human Bone Marrow-Derived Mesenchymal Stem Cells in Knee Osteoarthritis: A Randomized, Double-Blind, Controlled Trial. Cell Transplant. 2025;34:9636897241303275. doi: 10.1177/09636897241303275.
21. Wang X, Xu L, Wu Z, Lou L, Xia C, Miao H, et al. Exosomes of stem cells: a potential frontier in the treatment of osteoarthritis. Precis Clin Med. 2024;8(1):pbae032. doi: 10.1093/pcmedi/pbae032.
22. Zampogna B, Parisi FR, Ferrini A, Zampoli A, Papalia GF, Shanmugasundaram S, et al. Safety and efficacy of autologous adipose-derived stem cells for knee osteoarthritis in the elderly population: A systematic review. J Clin Orthop Trauma. 2024;59:102804. doi: 10.1016/j.jcot.2024.102804.
23. Han JH, Jung M, Chung K, Moon HS, Jung SH, Byun J. Intra-Articular Stromal Vascular Fraction and Mesenchymal Stem Cell Injections Show Variable Efficacy and Higher Potential Complications Compared to Corticosteroid and Hyaluronic Acid in Treatment of Knee Osteoarthritis: A Meta-Analysis of Randomized Controlled Trials. Arthroscopy. 2025:S0749-8063(25)00068-4. doi: 10.1016/j.arthro.2025.01.050.
24. ZoghAli M, Amini N, Babaei-Ghazani A, Forogh B, Joghataei MT, Babaei MR, et al. The Effects of Ultrasound-guided Corticosteroid Injection Compared to Mesenchymal Stem Cell Injection in Patients with Grade II and III Knee Osteoarthritis: A Randomized Double-blind Controlled Trial. Am J Phys Med Rehabil. 2025. doi: 10.1097/PHM.0000000000002691.
25. Soufan S, Al Khoury J, Hamdan Z, Rida MA. Intra-articular interventions in osteoarthritis: Navigating the landscape of hyaluronic acid, mesenchymal stem cells, and platelet-rich plasma. World J Orthop. 2024;15(8):704-712. doi: 10.5312/wjo.v15.i8.704.
26. Jin WS, Yin LX, Sun HQ, Zhao Z, Yan XF. Mesenchymal stem cells injection is more effective than hyaluronic acid injection in the treatment of knee osteoarthritis with similar safety: systematic review and meta-analysis. Arthroscopy. 2024:S0749-8063(24)00555-3. doi: 10.1016/j.arthro.2024.07.027.
27. Lamo-Espinosa JM, Suárez-López Del Amo Á, Núñez-Córdoba JM, Blanco JF, Sánchez M, Moreno V, et al. Effect of Hyaluronic Acid Compared to Platelet-Rich Plasma as Adjuvants to Bone Marrow Mesenchymal Stem Cell Treatment of Knee Osteoarthritis: Analysis from Two Clinical Trials. Diagnostics (Basel). 2025;15(3):309. doi: 10.3390/diagnostics15030309.
28. Quintero D, Perucca Orfei C, Kaplan LD, de Girolamo L, Best TM, Kouroupis D. The roles and therapeutic potential of mesenchymal stem/stromal cells and their extracellular vesicles in tendinopathies. Front Bioeng Biotechnol. 2023;11:1040762. doi: 10.3389/fbioe.2023.1040762.
29. Chen J, Wang Z, Yi M, Yang Y, Tian M, Liu Y, et al. Regenerative properties of bone marrow mesenchymal stem cell derived exosomes in rotator cuff tears. J Transl Med. 2025;23(1):47. doi: 10.1186/s12967-024-06029-2.
30. Gopinatth V, Boghosian T, Perugini JM, Smith MV, Knapik DM. Current Concepts in Orthobiologics for Achilles Tendon Injuries: A Critical Analysis Review. JBJS Rev. 2024;12(11). doi: 10.2106/JBJS.RVW.24.00144.
31. Vieira MHC, de Carvalho Schweich-Adami L, Oliveira RJ, Antoniolli-Silva ACMB. Effect of cell therapy with adipose-derived stem cells in the treatment of acute rupture of the Achilles tendon in humans. Cell Tissue Bank. 2024. doi: 10.1007/s10561-024-10141-4.
32. Schneider N, Sinnott M, Patel N, Joseph R. The Use of Platelet-Rich Plasma and Stem Cell Injections in Musculoskeletal Injuries. Cureus. 2024;16(5):e59970. doi: 10.7759/cureus.59970.
33. Wang X, Hu L, Wei B, Wang J, Hou D, Deng X. Regenerative therapies for femoral head necrosis in the past two decades: a systematic review and network meta-analysis. Stem Cell Res Ther. 2024;15(1):21. doi: 10.1186/s13287-024-03635-1.
34. Jia Z, Liu D, Xu J, Wang Q, Zhang L, Yin S, et al. An international analysis of stem cell research in intervertebral disc degeneration. Stem Cell Res. 2023;67:103044. doi: 10.1016/j.scr.2023.103044.
35. Manchikanti L, Knezevic E, Knezevic NN, Kaye AD, Atluri S, Sanapati MR, et al. Effectiveness of Intradiscal Regenerative Medicine Therapies for Long-Term Relief of Chronic Low Back Pain: A Systematic Review and Meta-Analysis. Pain Physician. 2024;27(10):E995-E1032.
36. Zhao Y, Xia Q, Zhu L, Xia J, Xiang S, Mao Q, et al. Mapping knowledge structure and themes trends of non-surgical treatment in intervertebral disc degeneration. Heliyon. 2024;10(17):e36509. doi: 10.1016/j.heliyon.2024.e36509.
37. DesRochers J, DesRochers R, Patel D, Andruszka C, Manchanda S, Ernazarov A, Mobley A. Mesenchymal stem cells and thermal annular procedures for discogenic pain: a systematic review with pooled analysis. Pain Manag. 2024. doi: 10.2217/pmt-2023-0107.
38. Randy R, Yosua K, Guntara A, Hardiansyah NP. Stem Cells Therapy as a Treatment for Discogenic Low Back Pain: A Systematic Review. Int J Spine Surg. 2025:86717. doi: 10.14444/86717.
39. Wang F, Cheung CW, Wong SSC. Regenerative medicine for the treatment of chronic low back pain: a narrative review. J Int Med Res. 2023;51(2):3000605231155777. doi: 10.1177/03000605231155777.
40. Ufondu W, Robinson CL, Hussain N, D'Souza RS, Karri J, Emerick T, Orhurhu VJ. Intradiscal Autologous Biologics for the Treatment of Chronic Discogenic Low Back Pain. Curr Pain Headache Rep. 2024. doi: 10.1007/s11916-024-01294-8.
41. Gupta A. Exosomes for the Management of Low Back Pain: A Review of Current Clinical Evidence. Cureus. 2024;16(4):e57539. doi: 10.7759/cureus.57539.
42. Navani A, Ambach M, Calodney A, Rosenthal R, Li G, Mahoney CB, Everts PA. The Safety and Effectiveness of Orthobiologic Injections for Discogenic Chronic Low Back Pain: A Multicenter Prospective, Crossover, Randomized Controlled Trial with 12 Months Follow-up. Pain Physician. 2024 Jan;27(1):E65-E77.
43. Leão Monteiro R. Future of low back pain: unravelling IVD components and MSCs' potential. Cell Regen. 2024;13(1):1. doi: 10.1186/s13619-023-00184-5.
44. Zhang WJ, Pi XW, Hu DX, Liu XP, Wu MM. Advances and challenges in cell therapy for neuropathic pain based on mesenchymal stem cells. Front Cell Dev Biol. 2025;13:1536566. doi: 10.3389/fcell.2025.1536566.
45. Yin Q, Zou T, Sun S, Yang D. Cell therapy for neuropathic pain. Front Mol Neurosci. 2023;16:1119223. doi: 10.3389/fnmol.2023.1119223.
46. Candido K, Prodromos C, Nenchev K. CT-Guided Foramen Ovale Injection of Mesenchymal Stem Cells: First Human Case Report of Trigeminal Neuralgia Relief. Curr Stem Cell Res Ther. 2024. doi: 10.2174/011574888X335230241111061649.
47. Kiabi FH, Khosravi T, Ahangar SG, Beiranvand S. The Importance of Stem Cells in the Treatment of Neuropathic Pain. Cent Nerv Syst Agents Med Chem. 2024. doi: 10.2174/0118715249328823241111101137.
48. Alizadeh SD, Jahani S, Rukerd MRZ, Tabrizi R, Masoomi R, Banihashemian SZ, et al. Human studies of the efficacy and safety of stem cells in the treatment of diabetic peripheral neuropathy: a systematic review and meta-analysis. Stem Cell Res Ther. 2024;15(1):442. doi: 10.1186/s13287-024-04033-3.
49. Wijayanti IAS, Adnyana IMO, Widyadharma IPE, Wiratnaya IGE, Mahadewa TGB, Astawa INM. Neuroinflammation mechanism underlying neuropathic pain: the role of mesenchymal stem cell in neuroglia. AIMS Neurosci. 2024;11(3):226-243. doi: 10.3934/Neuroscience.2024015.
50. Montagnoli TL, Santos AD, Sudo SZ, Gubert F, Vasques JF, Mendez-Otero R, et al. Perspectives on Stem Cell Therapy in Diabetic Neuropathic Pain. Neurol Int. 2024;16(5):933-944. doi: 10.3390/neurolint16050070.
51. D'Souza RS, Her YF, Hussain N, Karri J, Schatman ME, Calodney AK, et al. Evidence-Based Clinical Practice Guidelines on Regenerative Medicine Treatment for Chronic Pain: A Consensus Report from a Multispecialty Working Group. J Pain Res. 2024;17:2951-3001. doi: 10.2147/JPR.S480559.
52. Zhang J, Wu P, Wen Q. Optimization strategies for mesenchymal stem cell-based analgesia therapy: a promising therapy for pain management. Stem Cell Res Ther. 2024;15(1):211. doi: 10.1186/s13287-024-03828-8.
53. Xin GD, Liu XY, Fan XD, Zhao GJ. Exosomes repairment for sciatic nerve injury: a cell-free therapy. Stem Cell Res Ther. 2024;15(1):214. doi: 10.1186/s13287-024-03837-7.
54. Deng K, Hu DX, Zhang WJ. Application of cell transplantation in the treatment of neuropathic pain. Neuroscience. 2024:S0306-4522(24)00298-7. doi: 10.1016/j.neuroscience.2024.06.035.
55. Kataria S, Patel U, Yabut K, Patel J, Patel R, Patel S, et al. Recent Advances in Management of Neuropathic, Nociceptive, and Chronic Pain: A Narrative Review with Focus on Nanomedicine, Gene Therapy, Stem Cell Therapy, and Newer Therapeutic Options. Curr Pain Headache Rep. 2024. doi: 10.1007/s11916-024-01227-5.
56. Chang J, Yin XM, Zhang M, Liu JW, Zhao L. Bridging bioengineering and nanotechnology: Bone marrow derived mesenchymal stem cell-exosome solutions for peripheral nerve injury. World J Stem Cells. 2025;17(1):101161. doi: 10.4252/wjsc.v17.i1.101161.
57. Akhlaghpasand M, Tavanaei R, Hosseinpoor M, Heidari R, Mohammadi I, Chamanara M, et al. Effects of Combined Intrathecal Mesenchymal Stem Cells and Schwann Cells Transplantation on Neuropathic Pain in Complete Spinal Cord Injury: A Phase II Randomized Active-Controlled Trial. Cell Transplant. 2025;34:9636897241298128. doi: 10.1177/09636897241298128.
58. Zhang WJ, Chen D. Mesenchymal stem cell transplantation plays a role in relieving cancer pain. Front Pharmacol. 2024;15:1483716. doi: 10.3389/fphar.2024.1483716.r

CARDIOVASCULAR DISEASES

A causal relationship between inflammatory cytokines and cardiovascular diseases, including stable and unstable angina, myocardial infarction, and heart failure, has already been demonstrated (1). The regenerative and paracrine actions (anti-inflammatory and immunomodulatory) of stem cells/exosomes, reflected in inflammation and fibrosis control, preservation of cardiac muscle contractility, and stimulation of new blood vessel formation, have driven research into the role of regenerative medicine, particularly in ischemic heart disease (angina, myocardial infarction) and cardiomyopathy (heart failure). These conditions remain among the leading causes of morbidity and mortality worldwide, despite significant advances in technology, surgery, and cardiovascular pharmacology (2). However, It is important to clarify, that certain gaps remain to be addressed before establishing specific protocols, such as dosage, cell type, timing of application, and route of administration. Additionally, long-term parameters, such as survival rates, do not always yield consistent results. These discrepancies are often attributed to factors like the source of the applied cells, donor age, laboratory practices, and administration routes, among others. (3,4). Current research explores strategies to enhance the cardiac regenerative potential of stem cells/exosomes. These approaches include controlled-release methods, molecular or genetic modifications, and the use of biomaterials, all aimed at maximizing the beneficial effects of regenerative medicine (5,6).

REFRACTORY ANGINA

Referred to as refractory, this condition is characterized by persistent angina despite several months of standard treatment. Patients are often ineligible for revascularization due to the presence of diffuse coronary lesions or severe comorbidities. Stem cell therapy is emerging as a valuable approach for managing these patients, as supported by clinical trials (7). When comparing patients receiving standard treatment plus stem cells with those undergoing only optimal conventional management, studies report improvements in angina indicators and attack frequency, increased exercise tolerance, and a reduction in all-cause mortality, without a rise in adverse reactions among those treated with stem cells. Angina or ischemia with non-obstructive coronary artery disease (ANOCA/INOCA) are conditions with poorly understood pathophysiological mechanisms, though they are associated with microcirculatory dysfunction and spasms. In addition to conventional pharmacological treatment for angina, stem cell therapy represents a novel and promising therapeutic approach for these cases (8,9).



MYOCARDIAL INFARCTION (MI)

Cell death secondary to myocardial infarction (MI) triggers a strong inflammatory response aimed at repairing the cardiac muscle. However, this process also initiates ventricular remodeling, the duration and intensity of which determine the prognosis of the infarction. In other words, ventricular remodeling begins as an adaptive response but, when prolonged, leads to adverse consequences such as ventricular wall thinning and dilation, ultimately resulting in myocardial dysfunction. In this context, pharmacological therapy and established reperfusion strategies (thrombolysis, angioplasty, or surgical revascularization) offer only limited benefits (10). According to available evidence, the anti-inflammatory and immunomodulatory activity, on the one hand, and the regenerative activity, on the other, explain how stem cells/exosomes restore the balance between inflammation and repair, regulate cardiac remodeling, and improve infarction prognosis (11-15). Meta-analyses including randomized controlled clinical trials with thousands of patients who experienced a myocardial infarction (MI) and received timely surgery and/or conventional pharmacological treatment indicate that the addition of stem cells/exosomes is associated with significant clinical improvement and enhanced cardiac function parameters (ejection fraction, infarct size, hospital readmission rates, survival, and risk of major adverse events such as cardiovascular death, reinfarction, and stroke); patients with microvascular obstruction who suffer ST-elevation MI appear to represent a subgroup that benefits most from intracoronary stem cell application. The achievement of this level of evidence explains why an increasing number of experts consider regenerative therapy with stem cells/exosomes as a viable option to be included in myocardial infarction treatment protocols. Notably, in the treatment of heart failure and myocardial infarction, umbilical cord-derived stem cells have demonstrated more favorable outcomes compared to bone marrow-derived cells, with two doses proving more effective than a single dose (16-26).

CARDIOMYOPATHY (ISCHEMIC AND NONISCHEMIC)

As previously mentioned, ischemic injury and the subsequent death of cardiac muscle cells lead to cardiac fibrosis, in which damaged tissue is replaced by fibrotic scarring. While this scarring plays a crucial role in preventing ventricular wall rupture in the infarcted area, over time, it progressively extends to non-infarcted regions, ultimately worsening cardiac function. Despite optimal medical and surgical management, many patients with heart disease remain susceptible to a gradual process of myocardial damage, which can progressively impair the heart's ability to contract and relax. In other words, current treatment protocols may not fully prevent the decline in myocardial viability over time, potentially contributing to cardiomyopathy. Under these circumstances, it is unsurprising that the medical community has sought to explore the potential

benefits of stem cells/exosomes, given their anti-inflammatory, anti-fibrotic, angiogenic, and immunomodulatory properties (27) Since 2018, multiple meta-analyses have been published, encompassing dozens of studies involving thousands of patients with heart failure, systematically evaluating the effects of stem cell-based therapy. The findings can be summarized as follows: compared to conventionally treated controls, patients who received stem cell therapy showed significant improvements in nearly all clinical and paraclinical indicators of cardiac function, regardless of the underlying cause of heart failure. These improvements included heart failure severity classification, walking distance, quality of life, and overall mortality. Notably, no significant differences in the incidence of serious adverse events were observed between the treatment and control groups (28-34).

Heart failure with preserved ejection fraction (HFpEF) warrants special consideration, as its pathophysiology has been attributed to three primary mechanisms: a) microvascular damage resulting from comorbid conditions, b) low-grade cardiac inflammation in response to chronic mechanical stress, and c) dysfunction driven by intrinsic pro-inflammatory activity within the heart, potentially influenced by hereditary factors. Emerging evidence suggests that stem cell therapy plays a role in modulating cardiac remodeling and improving microcirculation in HFpEF, positioning it as a promising therapeutic option (35).

ATHEROSCLEROSIS AND PERIPHERAL ARTERIAL DISEASE

Atherosclerosis is a chronic inflammatory vascular disease that constitutes the pathological basis of peripheral, cerebrovascular, and cardiovascular disease (36). Atherosclerosis has both inflammatory and immune components, driven by cells and inflammatory markers that can be measured and used to assess the risk of atheromatous plaque progression (37). Due to their anti-inflammatory, immunomodulatory, and angiogenic properties (promoting the formation of new blood vessels), stem cells/exosomes play a key role in controlling atheroma formation and stabilizing established plaques, thereby reducing the risk of inflammation, rupture, and thrombus formation (38,39). For these reasons, regenerative therapy based on stem cells/exosomes represents an innovative approach to the treatment of atherosclerosis (40-44).

Moreover, in individuals with atherosclerotic ischemia of the lower limbs, stem cells have been reported to stimulate neovascularization and the development of collateral circulation, thereby improving blood supply to tissues. This effect has been associated with a reduction in amputation rates, even in patients with critical limb ischemia who are not candidates for revascularizations (45).

REFERENCES

1. Chen Y, Zhong A. Causal effects of inflammatory cytokines on cardiovascular diseases: Insights from genetic evidence. Heliyon. 2024 Jul 30;10(15):e35447. doi: 10.1016/j.heliyon.2024.e35447.

2. Sun CK. Editorial: Application of stem cells in the treatment of myocardial infarction. Front Cardiovasc Med. 2023;10:1333732. doi: 10.3389/fcvm.2023.1333732.

3. Abouzid MR, Ali K, Kamel I, Esteghamati S, Saleh A, Ghanim M. The Safety and Efficacy of Human Umbilical Cord-Derived Mesenchymal Stem Cells in Patients With Heart Failure and Myocardial Infarction: A Meta-Analysis of Clinical Trials. Cureus. 2023;15(11):e49645. doi: 10.7759/cureus.49645.

4. Barrère-Lemaire S, Vincent A, Jorgensen C, Piot C, Nargeot J, Djouad F. Mesenchymal stromal cells for improvement of cardiac function following acute myocardial infarction: a matter of timing. Physiol Rev. 2023. doi: 10.1152/physrev.00009.2023.

5. Yan W, Xia Y, Zhao H, Xu X, Ma X, Tao L. Stem cell-based therapy in cardiac repair after myocardial infarction: Promise, challenges, and future directions. J Mol Cell Cardiol. 2024;188:1-14. doi: 10.1016/j.yjmcc.2023.12.009.

6. An C, Zhao Y, Guo L, Zhang Z, Yan C, Zhang S, et al. Innovative approaches to boost mesenchymal stem cells efficacy in myocardial infarction therapy. Mater Today Bio. 2025;31:101476. doi: 10.1016/j.mtbio.2025.101476.

7. Chen Y, Ge Y, Chao T, Huan N, Liu W, Chu G, Wang C. Refractory angina pectoris: a 20-year (2003-2022) bibliometric analysis. Front Cardiovasc Med. 2023;10:1228201. doi: 10.3389/fcvm.2023.1228201.

8. Corban MT, Toya T, Albers D, Sebaali F, Lewis BR, Bois J, et al. IMPROvE-CED Trial: Intracoronary Autologous CD34+ Cell Therapy for Treatment of Coronary Endothelial Dysfunction in Patients With Angina and Nonobstructive Coronary Arteries. Circ Res. 2022;130(3):326-338. doi: 10.1161/CIRCRESAHA.121.319644.

9. Ashokprabhu ND, Quesada O, Alvarez YR, Henry TD. INOCA/ANOCA: Mechanisms and novel treatments. Am Heart J Plus. 2023;30:100302. doi: 10.1016/j.ahjo.2023.100302.

10. Chepeleva EV. Cell Therapy in the Treatment of Coronary Heart Disease. Int J Mol Sci. 2023;24(23):16844. doi: 10.3390/ijms242316844.

11. Cortés-Morales VA, Vázquez-González WG, Montesinos JJ, Moreno-Ruíz L, Salgado-Pastor S, Salinas-Arreola PM, et al. Human Bone Marrow Mesenchymal Stem Cells Promote the M2 Phenotype in Macrophages Derived from STEMI Patients. Int J Mol Sci. 2023;24(22):16257. doi: 10.3390/ijms242216257.

12. Yang Y, Wu A, Deng AN, Liu H, Lan Q, Mazhar M, et al. Macrophages after myocardial infarction: Mechanisms for repairing and potential as therapeutic approaches. Int Immunopharmacol. 2024;143(Pt 3):113562. doi: 10.1016/j.intimp.2024.113562.

13. Matta A, Ohlmann P, Nader V, Moussallem N, Carrié D, Roncalli J. A Review of Therapeutic Approaches for Post-Infarction Left Ventricular Remodeling. Curr Probl Cardiol. 2024:102562. doi: 10.1016/j.cpcardiol.2024.102562.

14. Yu T, Xu Q, Chen X, Deng X, Chen N, Kou MT, et al. Biomimetic nanomaterials in myocardial infarction treatment: Harnessing bionic strategies for advanced therapeutics. Mater Today Bio. 2024;25:100957. doi: 10.1016/j.mtbio.2024.100957.

15. Gao S, Li D, Wang B, Zhang H, Chen L. Two promising approaches in the treatment of myocardial infarction: stem cells and gene therapy. Front Cardiovasc Med. 2025;12:1540066. doi: 10.3389/fcvm.2025.1540066.

16. Ma J, Wang W, Zhang W, Xu D, Ding J, Wang F, et al. The recent advances in cell delivery approaches, biochemical and engineering procedures of cell therapy applied to coronary heart disease. Biomed Pharmacother. 2023;169:115870. doi: 10.1016/j.biopha.2023.115870.

17. Davidson SJ, Roncalli J, Surder D, Corti R, Chugh AR, Yang PC, et al. Microvascular Obstruction Identifies a Subgroup of Patients Who Benefit from Stem Cell Therapy Following ST-Elevation Myocardial Infarction. Am Heart J. 2023:S0002-8703(23)00037-6. doi: 10.1016/j.ahj.2023.02.004.

18. Attar A, Farjoud Kouhanjani M, Hessami K, Vosough M, Kojuri J, Ramzi M, et al. Effect of once versus twice intracoronary injection of allogeneic-derived mesenchymal stromal cells after acute myocardial infarction: BOOSTER-TAHA7 randomized clinical trial. Stem Cell Res Ther. 2023;14(1):264. doi: 10.1186/s13287-023-03495-1.

19. Peng C, Yan J, Jiang Y, Wu L, Li M, Fan X. Exploring Cutting-Edge Approaches to Potentiate Mesenchymal Stem Cell and Exosome Therapy for Myocardial Infarction. J Cardiovasc Transl Res. 2023. doi: 10.1007/s12265-023-10438-x.

20. Qin D, Wang X, Pu J, Hu H. Cardiac cells and mesenchymal stem cells derived extracellular vesicles: a potential therapeutic strategy for myocardial infarction. Front Cardiovasc Med. 2024;11:1493290. doi: 10.3389/fcvm.2024.1493290.

21. Li P. Comparative breakthrough: Umbilical cord mesenchymal stem cells *vs* bone marrow mesenchymal stem cells in heart failure treatment. World J Cardiol. 2024;16(12):776-780. doi: 10.4330/wjc.v16.i12.776.

22. Lee H, Cho HJ, Han Y, Lee SH. Mid- to long-term efficacy and safety of stem cell therapy for acute myocardial infarction: a systematic review and meta-analysis. Stem Cell Res Ther. 2024;15(1):290. doi: 10.1186/s13287-024-03891-1.

23. Safwan M, Bourgleh MS, Aldoush M, Haider KH. Tissue-source effect on mesenchymal stem cells as living biodrugs for heart failure: Systematic review and meta-analysis. World J Cardiol. 2024;16(8):469-483. doi: 10.4330/wjc.v16.i8.469.

24. Tonkin D, Yee-Goh A, Katare R. Healing the Ischaemic Heart: A Critical Review of Stem Cell Therapies. Rev Cardiovasc Med. 2023;24(4):122. doi: 10.31083/j.rcm2404122.

25. Abouzid MR, Umer AM, Jha SK, Akbar UA, Khraisat O, Saleh A, et al. Stem Cell Therapy for Myocardial Infarction and Heart Failure: A Comprehensive Systematic Review and Critical Analysis. Cureus. 2024;16(5):e59474. doi: 10.7759/cureus.59474.

26. Ali SA, Mahmood Z, Mubarak Z, Asad M, Sarfraz Chaudhri MT, Bilal L, et al. Assessing the Potential Benefits of Stem Cell Therapy in Cardiac Regeneration for Patients With Ischemic Heart Disease. Cureus. 2025;17(1):e76770. doi: 10.7759/cureus.76770.

27. Amirzadeh Gougheri K, Ahmadi A, Ahmadabadi MG, Babajani A, Yazdanpanah G, Bahrami S, et al. Exosomal Cargo: Pro-angiogeneic, anti-inflammatory, and regenerative effects in ischemic and non-ischemic heart diseases - A comprehensive review. Biomed Pharmacother. 2023;168:115801. doi: 10.1016/j.biopha.2023.115801.

28. Krishna Mohan GV, Tirumandyam G, Vemulapalli HS, Vajje J, Asif H, Saleem F. Mesenchymal Stem Cell Therapy for a Better Prognosis of Heart Failure: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Cureus. 2023;15(8):e43037. doi: 10.7759/cureus.43037.

29. Kavousi S, Hosseinpour A, Bahmanzadegan Jahromi F, Attar A. Efficacy of mesenchymal stem cell transplantation on major adverse cardiovascular events and cardiac function indices in patients with chronic heart failure: a meta-analysis of randomized controlled trials. J Transl Med. 2024;22(1):786. doi: 10.1186/s12967-024-05352-y.

30. Seth J, Sharma S, Leong CJ, Vaibhav V, Nelson P, Shokravi A, et al. The Use of Hematopoietic Stem Cells for Heart Failure: A Systematic Review. Int J Mol Sci. 2024;25(12):6634. doi: 10.3390/ijms25126634.

31. Ahmed ZT, Zain Al-Abeden MS, Al Abdin MG, Muqresh MA, Al Jowf GI, Eijssen LMT, Haider KH. Dose-response relationship of MSCs as living Bio-drugs in HFrEF patients: a systematic review and meta-analysis of RCTs. Stem Cell Res Ther. 2024;15(1):165. doi: 10.1186/s13287-024-03713-4.

32. Tao S, Yu L, Li J, Wu J, Yang D, Xue T, Zhang L, Xie Z, Huang X. Stem cell therapy for non-ischemic dilated cardiomyopathy: a systematic review and meta-analysis. Syst Rev. 2024;13(1):276. doi: 10.1186/s13643-024-02701-2.

33. Qayyum AA, Frljak S, Juhl M, Poglajen G, Zemljič G, Cerar A, et al. Mesenchymal stromal cells to treat patients with non-ischaemic heart failure: Results from SCIENCE II pilot study. ESC Heart Fail. 2024. doi: 10.1002/ehf2.14925.

34. Sawalha IA, Salih AQA, Bdour MA, Shimi RA, Slehat MA, Almansi A, et al. Safety and Efficacy of Transendocardial Stem Cells Therapy in Chronic Ischemic Heart Failure: A Systematic Review and Meta-analysis of Randomized Controlled Trials. Curr Cardiol Rev. 2025. doi: 10.2174/011573403X353157250115105436.

35. Domaszk O, Skwarek A, Wojciechowska M. In Search of the Holy Grail: Stem Cell Therapy as a Novel Treatment of Heart Failure with Preserved Ejection Fraction. Int J Mol Sci. 2023;24(5):4903. doi: 10.3390/ijms24054903.

36. Nguyen NT, Phan HT, Le PM, Nguyen LT, Do TT, Phan TT, et al. Safety and efficacy of autologous adipose tissue-derived stem cell transplantation in aging-related low-grade inflammation patients: a single-group, open-label, phase I clinical trial. Trials. 2024;25(1):309. doi: 10.1186/s13063-024-08128-3.

37. Sun S, Liu F, Fan F, Chen N, Pan X, Wei Z, Zhang Y. Exploring the mechanism of atherosclerosis and the intervention of traditional Chinese medicine combined with mesenchymal stem cells based on inflammatory targets. Heliyon. 2023;9(11):e22005. doi: 10.1016/j.heliyon.2023.e22005.

38. Dabravolski S, Sukhorukov VN, Glanz V, Pleshko E, Orekhov N, Sobenin I. Exosomes in Atherosclerosis: Role in the Pathogenesis and Targets for Therapy. Curr Med Chem. 2024. doi: 10.2174/0109298673302220240430173404.

39. Tariq H, Bukhari SZ, An R, Dong J, Ihsan A, Younis MR. Stem cell-derived exosome delivery systems for treating atherosclerosis: The new frontier of stem cell therapy. Mater Today Bio. 2024;30:101440. doi: 10.1016/j.mtbio.2024.101440.

40. Ma Y, Gu T, He S, He S, Jiang Z. Development of stem cell therapy for atherosclerosis. Mol Cell Biochem. 2023. doi: 10.1007/s11010-023-04762-8.

41. Pan Q, Chen C, Yang YJ. Top Five Stories of the Cellular Landscape and Therapies of Atherosclerosis: Current Knowledge and Future Perspectives. Curr Med Sci. 2023. doi: 10.1007/s11596-023-2818-2.

42. Saravanan S, Palaniyandi T, Palaniappan NA, Rajinikanth S, Shanmugam R, Wahab MRA. Emerging Therapeutic and Diagnostic Strategies for Coronary Artery Disease: Current Trends and Future Perspectives. Curr Probl Cardiol. 2024:102863. doi: 10.1016/j.cpcardiol.2024.102863.

43. Yuce K. The Application of Mesenchymal Stem Cells in Different Cardiovascular Disorders: Ways of Administration, and the Effectors. Stem Cell Rev Rep. 2024. doi: 10.1007/s12015-024-10765-9.

44. Egea V. Caught in action: how MSCs modulate atherosclerotic plaque. Front Cell Dev Biol. 2024;12:1379091. doi: 10.3389/fcell.2024.1379091.

45. Park YM, Park JK, Kim HS, Yang SS, Kim JW, Kim DI. A Phase 1/2a Clinical Trial to Evaluate the Efficacy and Safety of Allogenic Adipose Tissue-Derived Mesenchymal Stem Cell Clusters in Patients with Critical Limb Ischemia. Int J Stem Cells. 2025. doi: 10.15283/ijsc25002.

PULMONARY DISEASES

The lungs possess an extraordinary capacity for self-repair but are exposed to numerous harmful environmental and endogenous factors. These factors contribute to the development of obstructive, restrictive, and inflammatory diseases, both acute and chronic, ranging from pneumonia and acute respiratory distress syndrome (ARDS) to asthma, chronic obstructive pulmonary disease (COPD), pulmonary hypertension, and pulmonary fibrosis. With the rising global prevalence of these diseases, their high morbidity and mortality, and the limited treatment options for some, regenerative medicine, based on stem cells/exosomes, has gained significant attention. By fulfilling a dual role in mitigating inflammation-related damage and promoting lung regeneration. Clinical research is rapidly expanding, with growing evidence of its safety and efficacy reshaping the medical landscape (1-4). However, it is important to note that in the advanced stages of these diseases, the benefits of regenerative medicine remain limited. Furthermore, consensus has yet to be reached on factors such as the optimal cell source, dosage, administration routes, and treatment frequency, among others.

Viral pneumonia is the leading cause of ***acute respiratory distress syndrome*** (ARDS). Stem cells/exosomes from diverse sources have demonstrated benefits in controlling the inflammatory cascade triggered in ARDS (including COVID-19 and H1N1 influenza) by reducing the expression of pro-inflammatory cytokines responsible for lung tissue damage (5-9). A recent systematic review and meta-analysis on the role of stem cells in ARDS, involving hundreds of patients from randomized controlled trials, reported the following findings: improved clinical and pulmonary function, reduced inflammation markers and mortality, no increase in adverse events, and no statistically significant differences in ICU stay duration or ventilator-free days (10).

Pulmonary fibrosis is a chronic, progressive disease characterized by lung tissue remodeling, fibrous tissue accumulation, scar formation, and consequent loss of lung elasticity (11). Stem cells/exosomes, administered through inhalation or intravenous infusion, have shown anti-fibrotic activity in the lungs. Recent studies suggest that this therapy mitigates both idiopathic pulmonary

fibrosis (of unknown cause) and fibrosis secondary to ARDS, such as post-COVID-19 pulmonary fibrosis, a recognized complication of long COVID (12-19).

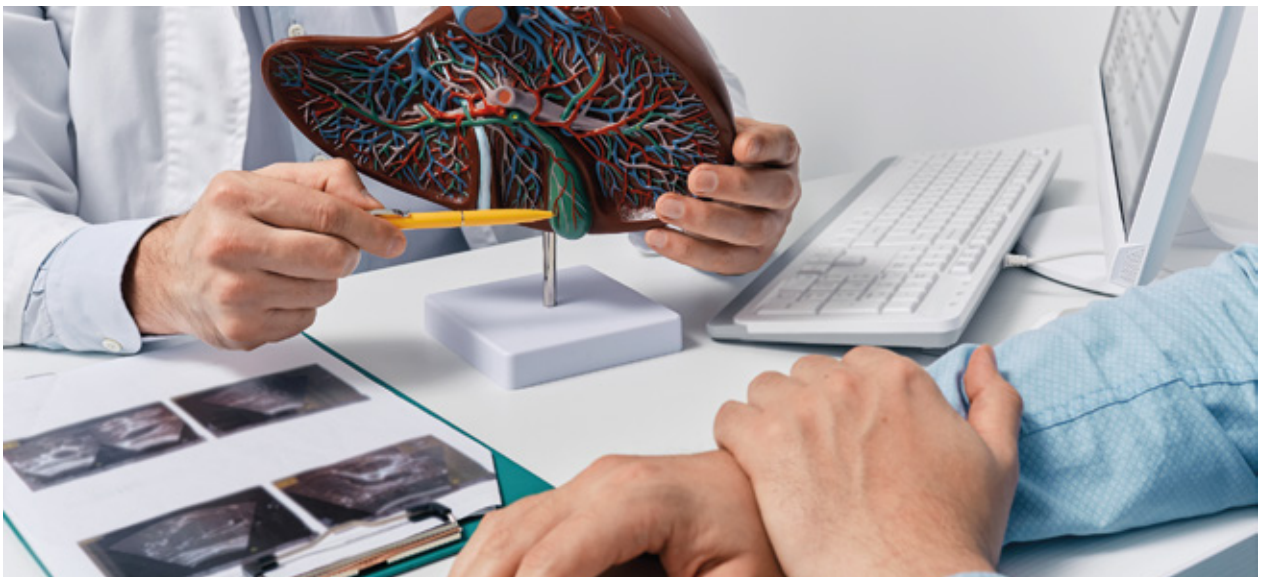
In ***asthma***, the dynamic balance between Th1 and Th2 lymphocytes is disrupted, leading to inflammation, hyperreactivity, and airway remodeling (20). Although proven, effective, and safe treatment protocols exist, a small group of patients does not achieve therapeutic goals with current options (21). Stem cells/exosomes help restore the balance between these lymphocyte populations and have demonstrated benefits in asthma by controlling inflammation and airway remodeling. The potential benefits of nebulized airway delivery are worth highlighting. An interesting *in vitro* finding revealed that exposing blood from asthma patients to stem cell-derived exosomes induced immunomodulatory effects, evidenced by the inhibition of pro-inflammatory cytokines and the expansion of anti-inflammatory lymphocytes (22-25).

Stem cells and exosomes have also demonstrated a favorable safety and efficacy profile in ***COPD*** (26,27). A randomized controlled clinical trial in patients with stage II to IV COPD, which was highlighted in an editorial by JAMA (28), found that airway-administered stem cells improved lung function. Six months post-treatment, patients who received stem cells showed enhanced pulmonary function and increased six-minute walk distance, whereas the control group experienced a decline. Adverse events were minimal. Notably, the editorial emphasized that, until now, lung damage caused by COPD was considered irreversible.

REFERENCES

1. Hu Z, Zhu L, Zhu Y, Xu Y. Mesenchymal Stem Extracellular Vesicles in Various Respiratory Diseases: A New Opportunity. J Inflamm Res. 2024;17:9041-9058. doi: 10.2147/JIR.S480345.
2. Meng M, Zhang WW, Chen SF, Wang DR, Zhou CH. Therapeutic utility of human umbilical cord-derived mesenchymal stem cells-based approaches in pulmonary diseases: Recent advancements and prospects. World J Stem Cells. 2024;16(2):70-88. doi: 10.4252/wjsc.v16.i2.70.
3. Yuan D, Bao Y, El-Hashash A. Mesenchymal stromal cell-based therapy in lung diseases; from research to clinic. Am J Stem Cells. 2024;13(2):37-58. doi: 10.62347/JAWM2040.
4. Liang X, Li Y, Wu Y, Wu T, Huang D, Tang Z, et al. Human umbilical cord mesenchymal stem cell-derived microvesicles alleviate pulmonary fibrosis by inhibiting monocyte–macrophage migration through ERK1/2 signaling-mediated suppression of CCL2 expression. Stem Cell Res Ther. 2025;16(1):145. doi: 10.1186/s13287-025-04266-w.
5. Liang TY, Lu LH, Tang SY, Zheng ZH, Shi K, Liu JQ. Current status and prospects of basic research and clinical application of mesenchymal stem cells in acute respiratory distress syndrome. World J Stem Cells. 2023;15(4):150-164. doi: 10.4252/wjsc.v15.i4.150.
6. Liang D, Liu C, Yang M. Mesenchymal stem cells and their derived exosomes for ALI/ARDS: A promising therapy. Heliyon. 2023;9(10):e20387. doi: 10.1016/j.heliyon.2023.e20387.
7. Liang J, Dai W, Xue S, Wu F, Cui E, Pan R. Recent progress in mesenchymal stem cell-based therapy for acute lung injury. Cell Tissue Bank. 2024. doi: 10.1007/s10561-024-10129-0.
8. Guo CY, Wang Y, Feng Q, Sun LJ, Feng YM, Dong YH, et ak. Umbilical Cord Mesenchymal Stem Cells Could Reduce Lung Damage Caused by H1N1 Influenza Virus Infection. J Med Virol. 2025;97(2):e70214. doi: 10.1002/jmv.70214.
9. Wang S, Yang T, Li T, Shi L, Xu R, Zhang C, et al. Safety and efficacy of human umbilical cord-derived mesenchymal stem cells in COVID-19 patients: A real-world observation. Chin Med J (Engl). 2025. doi: 10.1097/CM9.0000000000003459.
10. Fang L, Hu F, Li H, Chang W, Liu L. Efficacy and safety of mesenchymal stem cell therapy for acute respiratory distress syndrome-a systematic review and meta-analysis. J Thorac Dis. 2024;16(9):5802-5814. doi: 10.21037/jtd-24-281.
11. Liang X, Li Y, Wu Y, Wu T, Huang D, Tang Z, et al. Human umbilical cord mesenchymal stem cell-derived microvesicles alleviate pulmonary fibrosis by inhibiting monocyte–macrophage migration through ERK1/2 signaling-mediated suppression of CCL2 expression. Stem Cell Res Ther. 2025;16(1):145. doi: 10.1186/s13287-025-04266-w.
12. Zhang H, Zhu Q, Ji Y, Wang M, Zhang Q, Liu W, et al. hucMSCs treatment prevents pulmonary fibrosis by reducing circANKRD42-YAP1-mediated mechanical stiffness. Aging (Albany NY). 2023;15. doi: 10.18632/aging.204805.
13. Efimenko AY, Shmakova AA, Popov VS, Basalova NA, Vigovskiy MA, Grigorieva OA, et al. Mesenchymal stem/stromal cells alleviate early-stage pulmonary fibrosis in a uPAR-dependent manner. Cell Biol Int. 2024. doi: 10.1002/cbin.12222.
14. Le NT, Dunleavy MW, Kumar RD, Zhou W, Bhatia SS, El-Hashash AH. Cellular therapies for idiopathic pulmonary fibrosis: current progress and future prospects. Am J Stem Cells. 2024;13(4):191-211. doi: 10.62347/DAKS5508.
15. Yang Y, Lv M, Xu Q, Wang X, Fang Z. Extracellular Vesicles in Idiopathic Pulmonary Fibrosis: Pathogenesis, Biomarkers and Innovative Therapeutic Strategies. Int J Nanomedicine. 2024;19:12593-12614. doi: 10.2147/IJN.S491335.
16. Duong-Quy S, Nguyen Hai C, Huynh-Anh T, Nguyen-Nhu V. Tackling pulmonary fibrosis risks in post-COVID-19: cutting-edge treatments. Expert Opin Pharmacother. 2024. doi: 10.1080/14656566.2024.2438322.
17. Silverstein E, Richmann M, Tyl D, Fiaoni A, Pfeifer K, Moussa H, et al. The Application of Mesenchymal Stem Cell Therapy in Treating Pulmonary Fibrosis: A Scoping Review. Cureus. 2024;16(11):e74611. doi: 10.7759/cureus.74611.
18. Zhang Z, Shan XY, Liang C, Zhao L, Shan XQ. Microvesicles derived from mesenchymal stem cells: A promising therapeutic strategy for acute respiratory distress syndrome-related pulmonary fibrosis? World J Stem Cells. 2025;17(1):101036. doi: 10.4252/wjsc.v17.i1.101036.
19. Wan R, Liu Y, Yan J, Lin J. Cell therapy: A beacon of hope in the battle against pulmonary fibrosis. FASEB J. 2025;39(2):e70356. doi: 10.1096/fj.202402790R.
20. Wang J, Yan K, Ma L, Yan X, Meng Z, Li JA, et al. Notch Signaling Pathway Interfering as a Possible Asthma Treatment: A Narrative Review. J Asthma Allergy. 2025;18:437-446. doi: 10.2147/JAA.S504925.
21. Huang S, Li Y, Zeng J, Chang N, Cheng Y, Zhen X, et al. Mesenchymal Stem/Stromal Cells in Asthma Therapy: Mechanisms and Strategies for Enhancement. Cell Transplant. 2023;32:9636897231180128. doi: 10.1177/09636897231180128.
22. Sadeghi M, Mohammadi M, Tavakol Afshari J, Iranparast S, Ansari B, Dehnavi S. Therapeutic potential of mesenchymal stem cell-derived exosomes for allergic airway inflammation. Cell Immunol. 2024;397-398:104813. doi: 10.1016/j.cellimm.2024.104813.
23. Jung JH, Kang SA, Park JH, Kim SD, Yu HS, Mun SJ, Cho KS. Immunomodulatory Effect of Adipose Stem Cell-Derived Extra-Cellular Vesicles on Cytokine Expression and Regulatory T Cells in Patients with Asthma. Int J Mol Sci. 2024;25(19):10524. doi: 10.3390/ijms251910524.
24. Chen S, Gao J, Zhang T. From mesenchymal stem cells to their extracellular vesicles: Progress and prospects for asthma therapy. Asian J Pharm Sci. 2024;19(4):100942. doi: 10.1016/j.ajps.2024.100942.
25. Chen QH, Zheng JY, Wang DC. Asthma and stem cell therapy. World J Stem Cells. 2025;17(2):103599. doi: 10.4252/wjsc.v17.i2.103599.
26. Singh PV, Singh PV, Anjankar A. Harnessing the Therapeutic Potential of Stem Cells in the Management of Chronic Obstructive Pulmonary Disease: A Comprehensive Review. Cureus. 2023;15(8):e44498. doi: 10.7759/cureus.44498.
27. Lai S, Guo Z. Stem cell therapies for chronic obstructive pulmonary disease: mesenchymal stem cells as a promising treatment option. Stem Cell Res Ther. 2024;15(1):312. doi: 10.1186/s13287-024-03940-9.
28. Anderer S. Stem Cell Transplants Might Boost Lung Function in People With COPD. JAMA. 2024. doi: 10.1001/jama.2024.4447.

LIVER DISEASES



Although the liver possesses a remarkable regenerative capacity, viral infections, drugs, toxins, metabolic disorders, and genetic or immune diseases can still cause acute liver failure or lead to chronic inflammation and cirrhosis, even with appropriate medical and surgical treatment (1) For some patients, liver transplantation is not a viable option due to donor shortages, immunosuppression-related complications, surgical complexity, and high costs.

Metabolic-associated fatty liver disease is the most common chronic liver condition and can progress to steatohepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma. While treatments have been approved for these conditions, their effectiveness remains limited, which is unsurprising given the intricate metabolic, inflammatory, and immune pathways driving disease progression (2) It is now widely accepted that an abnormal immune response plays a critical role in the onset and progression of nearly all liver diseases. A striking example is the decline in lymphocytes and the loss of T-cell function, which are strong predictors of imminent acute liver failure in patients with cirrhosis. As a result, hepatology research is increasingly focused on strategies to restore immune homeostasis. Beyond their regenerative properties, stem cells/exosomes exhibit potent immunomodulatory, anti-inflammatory, antioxidant, and anti-fibrotic activity. As a result, regenerative medicine has emerged as a promising therapeutic option for several liver diseases, including metabolic-associated fatty liver disease, non-alcoholic and alcoholic liver disease, viral and autoimmune hepatitis, acute-on-chronic liver failure, and cirrhosis (3-14).

Another clinically significant factor is the association between non-alcoholic fatty liver disease and insulin resistance, obesity, diabetes, dyslipidemia, hypertension, and cardiovascular disease Complementing existing pharmacological and lifestyle interventions for this complex metabolic and cardiovascular dysfunction, stem cell- and exosome-based therapy is emerging as a highly cost-effective and safe treatment option (15,16).

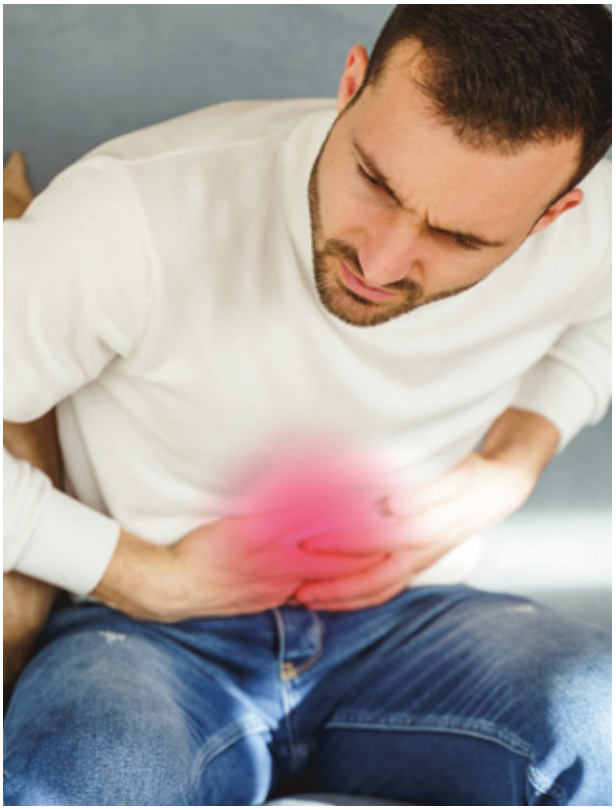
Extensive preclinical evidence demonstrates the ability of stem cells to differentiate into liver cells, highlighting their anti-inflammatory, antifibrotic, and immunoregulatory properties, as well as their therapeutic effects on acute liver failure in different animal models (17). The effectiveness and safety of stem cells/exosomes have been confirmed in multiple clinical trials and large meta-analyses involving thousands of patients. These studies consistently demonstrate benefits in the treatment of fatty liver disease, cirrhosis at various stages, and acute liver failure, with biochemical, histological, functional, and clinical improvements. The main reported benefits can be summarized as follows (18-22): a) clinical improvement of symptoms such as edema, fatigue, anorexia, and abdominal distension;
b) enhanced biochemical parameters, including increased serum albumin levels (reflecting improved protein synthesis), better coagulation function, total bilirubin reduction, and improved enzyme activity related to carbohydrate and lipid metabolism; c) reduction in MELD scores, which assess disease severity; d) increased survival rates. e) decreased incidence of liver cancer, although this effect varies across studies; f) no severe adverse events were reported in any of the included studies.

REFERENCES

1. Rajpurohit S, Musunuri B, Mohan PB, Bhat G, Shetty S. Factors Affecting and Promoting Health-related Quality of Life in Patients With Liver Cirrhosis: An Underestimated Domain in Patient Care. J Clin Exp Hepatol. 2024;14(1):101264. doi: 10.1016/j.jceh.2023.07.417.
2. Wang J, Bao S, An Q, Li C, Feng J. Roles of extracellular vesicles from different origins in metabolic-associated fatty liver disease: progress and perspectives. Front Immunol. 2025;16:1544012. doi: 10.3389/fimmu.2025.1544012.
3. Yang X, Li Q, Liu W, Zong C, Wei L, Shi Y, Han Z. Mesenchymal stromal cells in hepatic fibrosis/cirrhosis: from pathogenesis to treatment. Cell Mol Immunol. 2023. doi: 10.1038/s41423-023-00983-5.
4. Yi Q, Yang J, Wu Y, Wang Y, Cao Q, Wen W. Immune microenvironment changes of liver cirrhosis: emerging role of mesenchymal stromal cells. Front Immunol. 2023;14:1204524. doi: 10.3389/fimmu.2023.1204524.
5. Lan T, Li S, Yu H, Kostallari E, Gao J. Editorial: Community series in hepatic immune response underlying liver cirrhosis and portal hypertension, volume II. Front Immunol. 2023;14:1305666. doi: 10.3389/fimmu.2023.1305666.
6. Chen L, Zhang N, Huang Y, Zhang Q, Fang Y, Fu J, et al. Multiple Dimensions of using Mesenchymal Stem Cells for Treating Liver Diseases: From Bench to Beside. Stem Cell Rev Rep. 2023. doi: 10.1007/s12015-023-10583-5.
7. Korkida F, Stamatopoulou A, Roubelakis MG. Recent Advances in Mesenchymal Stem/Stromal Cell-Based Therapy for Alcohol-Associated Liver Disease and Non-alcoholic Fatty Liver Disease. Stem Cells Transl Med. 2023:szad082. doi: 10.1093/stcltm/szad082.
8. Jin YX, Hu HQ, Zhang JC, Xin XY, Zhu YT, Ye Y, Li D. Mechanism of mesenchymal stem cells in liver regeneration: Insights and future directions. World J Stem Cells. 2024;16(9):842-845. doi: 10.4252/wjsc.v16.i9.842.
9. Gao FQ, Zhu JQ, Feng XD. Innovative mesenchymal stem cell treatments for fatty liver disease. World J Stem Cells. 2024;16(9):846-853. doi: 10.4252/wjsc.v16.i9.846.
10. Wu L, Zhang L, Huang M, Wu Y, Jin S, Zhang Y, et al. Mesenchymal Stem Cell-Derived Exosomes: Emerging as a Promising Cell-Free Therapeutic Strategy for Autoimmune Hepatitis. Biomolecules. 2024;14(11):1353. doi: 10.3390/biom14111353.
11. Jiang Y, Yusoff NM, Du J, Moses EJ, Lin JT. Current perspectives on mesenchymal stem cells as a potential therapeutic strategy for non-alcoholic fatty liver disease. World J Stem Cells. 2024;16(7):760-772. doi: 10.4252/wjsc.v16.i7.760.
12. Mladenović D, Vesković M, Šutulović N, Hrnčić D, Stanojlović O, Radić L, et al. Adipose-derived extracellular vesicles - a novel cross-talk mechanism in insulin resistance, non-alcoholic fatty liver disease, and polycystic ovary syndrome. Endocrine. 2024. doi: 10.1007/s12020-024-03702-w.
13. Hong J, Kim YH. Cutting-edge biotherapeutics and advanced delivery strategies for the treatment of metabolic dysfunction-associated steatotic liver disease spectrum. J Control Release. 2025:S0168-3659(25)00114-2. doi: 10.1016/j.jconrel.2025.02.008.
14. Chen Y, Yang F, Wang Y, Shi Y, Liu L, Luo W, et al. Mesenchymal stem cell-derived small extracellular vesicles reduced hepatic lipid accumulation in MASLD by suppressing mitochondrial fission. Stem Cell Res Ther. 2025;16(1):116. doi: 10.1186/s13287-025-04228-2.
15. Nandula SR, Nylen ES, Sen S. Novel Therapeutics in Nonalcoholic Fatty Liver Disease: A Focus on Adult Stem Cells. Metab Syndr Relat Disord. 2023. doi: 10.1089/met.2022.0069.
16. Yi S, Cong Q, Zhu Y, Xu Q. Mechanisms of Action of Mesenchymal Stem Cells in Metabolic-Associated Fatty Liver Disease. Stem Cells Int. 2023;2023:3919002. doi: 10.1155/2023/3919002.
17. Skuratov AG, Osipov BB, Lyzikov AN, Zinovkin DA, Adam IM, Kaplan ML, et al. Use of Mesenchymal Stem Cell Transplantation as a Treatment for Liver Cirrhosis in Animal Models. Cureus. 2024;16(10):e71720. doi: 10.7759/cureus.71720.
18. Xie Y, Li Y, Yao J, Song X, Wang H, Zhang J, Li X. Protein Lactylation Modification and Proteomics Features in Cirrhosis Patients after UC-MSC Treatment. Curr Issues Mol Biol. 2023;45(10):8444-8460. doi: 10.3390/cimb45100532.
19. Lu W, Qu J, Yan L, Tang X, Wang X, Ye A, et al. Efficacy and safety of mesenchymal stem cell therapy in liver cirrhosis: a systematic review and meta-analysis. Stem Cell Res Ther. 2023;14(1):301. doi: 10.1186/s13287-023-03518-x.
20. Wang H, Yao W, Wang Y, Dong H, Dong T, Zhou W, et al. Meta-analysis on last ten years of clinical injection of bone marrow-derived and umbilical cord MSC to reverse cirrhosis or rescue patients with acute-on-chronic liver failure. Stem Cell Res Ther. 2023;14(1):267. doi: 10.1186/s13287-023-03494-2.
21. Wang Z, Yao L, Hu X, Yuan M, Chen P, Liu P, et al. Advancements in mesenchymal stem cell therapy for liver cirrhosis: Unveiling origins, treatment mechanisms, and current research frontiers. Tissue Cell. 2023;84:102198. doi: 10.1016/j.tice.2023.102198.
22. Li Z, Zhou X, Han L, Shi M, Xiao H, Lin M, et al. Human Umbilical Cord Blood-Derived Mesenchymal Stem Cell Transplantation for Patients with Decompensated Liver Cirrhosis. J Gastrointest Surg. 2023. doi: 10.1007/s11605-022-05528-1.

INFLAMMATORY BOWEL DISEASE (IBD)

This includes ***ulcerative colitis*** (UC) and ***Crohn's disease*** (CD). Both conditions share an autoimmune disorder in which different immune cells and mediators attack the digestive tract, leading to chronic inflammation, gut microbiota alterations, and intestinal tissue damage. Consequently, treatment focuses on immune system normalization and inflammation control (1,2). However, despite the growing availability of anti-inflammatory and immunosuppressive drugs, up to 30% of patients with IBD fail to respond to existing treatment protocols, and up to half of those who initially benefit eventually lose their response over time (3). In this context, stem cells/exosomes have been investigated for their capacity to promote tissue regeneration, exert paracrine effects (by releasing molecules that mitigate damage and support gut microbiota balance), regulate immune responses, and reduce inflammation (4,5).



The benefits of stem cell and exosome therapy for IBD have been confirmed in numerous clinical trials and meta-analyses involving thousands of patients, with the strongest evidence in CD, including severe, refractory cases with fistula formation (ano/rectal/vaginal). Reported clinical and paraclinical outcomes include extended remission duration, histological and radiological improvements with signs of tissue regeneration, reduced hospitalizations and surgeries, and a safety profile comparable to conventional therapy (6-21).

Key Considerations: a) the best outcomes were observed in patients with a disease duration of under five years, with complete remission associated with disease evolution under three years (22); b) while evidence on potential interactions between stem cells and conventional drugs remains inconclusive, studies suggest that combining stem cells with glucocorticoids or azathioprine (and possibly other medications) enhances therapeutic benefits in IBD (23-25); c) in an animal model of ulcerative colitis, exosomes achieved better outcomes than infliximab (26).

REFERENCES

1. Liao HJ, Hsu PN. Immunomodulatory effects of extracellular vesicles from mesenchymal stromal cells: Implication for therapeutic approach in autoimmune diseases. Kaohsiung J Med Sci. 2024. doi: 10.1002/kjm2.12841.

2. Kwon SJ, Khan MS, Kim SG. Intestinal Inflammation and Regeneration-Interdigitating Processes Controlled by Dietary Lipids in Inflammatory Bowel Disease. Int J Mol Sci. 2024;25(2):1311. doi: 10.3390/ijms25021311.

3. Shi MY, Liu L, Yang FY. Strategies to improve the effect of mesenchymal stem cell therapy on inflammatory bowel disease. World J Stem Cells. 2022;14(9):684-699. doi: 10.4252/wjsc.v14.i9.684.

4. Tian CM, Zhang Y, Yang MF, Xu HM, Zhu MZ, Yao J, et al. Stem Cell Therapy in Inflammatory Bowel Disease: A Review of Achievements and Challenges. J Inflamm Res. 2023;16:2089-2119. doi: 10.2147/JIR.S400447.

5. Saadh MJ, Mikhailova MV, Rasoolzadegan S, Falaki M, Akhavanfar R, Gonzáles JLA, et al. Therapeutic potential of mesenchymal stem/stromal cells (MSCs)-based cell therapy for inflammatory bowel diseases (IBD) therapy. Eur J Med Res. 2023;28(1):47. doi: 10.1186/s40001-023-01008-7.

6. Lightner AL, Dadgar N, Matyas C, Elliott K, Fulmer C, Khaitan N, et al. A phase IB/IIA study of remestemcel-L, an allogeneic bone marrow-derived mesenchymal stem cell product, for the treatment of medically refractory ulcerative colitis: an interim analysis. Colorectal Dis. 2022;24(11):1358-1370. doi: 10.1111/codi.16239.

7. Cheng F, Huang Z, Wei W, Li Z. Efficacy and safety of mesenchymal stem cells in the treatment of perianal fistulas in Crohn's disease: a meta-analysis of randomized controlled trials. Rev Esp Enferm Dig. 2023. doi: 10.17235/reed.2023.9213/2022.

8. Li A, Liu S, Li L, Yu M. Mesenchymal Stem Cells Versus Placebo for Perianal Fistulizing Crohn's Disease: A Systemic Review and Meta-Analysis. Surg Innov. 2023:15533506231157167. doi: 10.1177/15533506231157167.

9. Deng C, Zhang H, Li Y, Cheng X, Liu Y, Huang S, et al. Exosomes derived from mesenchymal stem cells containing berberine for ulcerative colitis therapy. J Colloid Interface Sci. 2024;671:354-373. doi: 10.1016/j.jcis.2024.05.162.

10. Karki C, Hantsbarger G, Turkstra E, Fenu E, Genenz K, Gilaberte I, Panés J. Predictive modeling to evaluate long-term treatment effectiveness of darvadstrocel in patients with complex perianal fistulas in Crohn's disease. BMC Gastroenterol. 2024;24(1):479. doi: 10.1186/s12876-024-03513-3.

11. Bacsur P, Shaham D, Serclova Z, Resál T, Farkas B, Sarlós P, et al. Evaluation of the Effectiveness and Safety of Mesenchymal Stem Cell Treatment in Fistulising Crohn's Disease: An International Real-Life Retrospective Multicentre Cohort Study. Aliment Pharmacol Ther. 2024. doi: 10.1111/apt.18359.

12. Bertin L, Crepaldi M, Zanconato M, Lorenzon G, Maniero D, De Barba C, et al. Refractory Crohn's Disease: Perspectives, Unmet Needs and Innovations. Clin Exp Gastroenterol. 2024;17:261-315. doi: 10.2147/CEG.S434014.

13. Taxonera C, García-Brenes MA, Olivares D, López-García ON, Zapater R, Alba C. Darvadstrocel for complex perianal fistulas in Crohn's disease: A systematic review and meta-analysis. United European Gastroenterol J. 2024. doi: 10.1002/ueg2.12673.

14. Hadizadeh A, Akbari-Asbagh R, Heirani-Tabasi A, Soleimani M, Gorovanchi P, Ebrahimi Daryani N, et al. Localized Administration of Mesenchymal Stem Cell-Derived Exosomes for the Treatment of Refractory Perianal Fistula in Crohn's Disease Patients: A Phase II Clinical Trial. Dis Colon Rectum. 2024. doi: 10.1097/DCR.0000000000003502.

15. Thangavelu L, Mohan S, Alfaifi HA, Farasani A, Menon SV, Bansal P, et al. Safety and efficacy of stem cell therapy for Crohn's disease: An umbrella review of systematic reviews. Int J Surg. 2024. doi: 10.1097/JS9.0000000000002104.

16. Qiu Y, Li C, Sheng S. Efficacy and safety of stem cell therapy for Crohn's disease: a meta-analysis of randomized controlled trials. Stem Cell Res Ther. 2024;15(1):28. doi: 10.1186/s13287-024-03637-z.

17. Mazzaro MC, de Paula AEC, Pascoal LB, Genaro LM, Pereira IM, Rodrigues BL, et al. Optimizing Treatment Outcomes in Crohn's Disease: A Comprehensive Systematic Review and Meta-Analysis of Regenerative Therapies with Emphasis on Platelet-Rich Plasma. Pharmaceuticals (Basel). 2024;17(11):1519. doi: 10.3390/ph17111519.

18. Herreros MD, Ramirez JM, Otero-Piñeiro AM, Martí-Gallostra M, Badiola I, Enríquez-Navascues JM, et al. Use of Darvadstrocel (Allogenic Stem Cell Therapy) for Crohn's Fistulas in Real Clinical Practice: The National Project to Implement Mesenchymal Stem Cell for the Treatment of Perianal Crohn's Fistula (the PRIME Study). Dis Colon Rectum. 2024. doi: 10.1097/DCR.0000000000003216.

19. Greco R, Alexander T, Del Papa N, Müller F, Saccardi R, Sanchez-Guijo F, et al. Innovative cellular therapies for autoimmune diseases: expert-based position statement and clinical practice recommendations from the EBMT practice harmonization and guidelines committee. EClinicalMedicine. 2024;69:102476. doi: 10.1016/j.eclinm.2024.102476.

20. Guisado D, Talware S, Wang X, Davis A, Fozilov E, Etra A, et al. Reparative immunological consequences of stem cell transplantation as a cellular therapy for refractory Crohn's disease. Gut. 2025:gutjnl-2024-333558. doi: 10.1136/gutjnl-2024-333558.

21. Bhatnagar P, Elhariri S, Burud IAS, Eid N. Perianal fistulizing Crohn's disease: Mechanisms and treatment options focusing on cellular therapy. World J Gastroenterol. 2025;31(9):100221. doi: 10.3748/wjg.v31.i9.100221.

22. Fathallah N, Siproudhis L, Akaffou M, Haouari MA, Landemaine A, Pommaret E, et al. Allogenic stem cells for Crohn's anal fistulas: Treating early improves the deep remission rate. Colorectal Dis. 2023. doi: 10.1111/codi.16782.

23. Jafar H, Alqudah D, Rahmeh R, Al-Hattab D, Ahmed K, Rayyan R, et al. Safety and Potential Efficacy of Expanded Umbilical Cord-Derived Mesenchymal Stromal Cells in Luminal Ulcerative Colitis Patients. Stem Cells Dev. 2024. doi: 10.1089/scd.2024.0102.

24. Wei S, Li M, Wang Q, Zhao Y, Du F, Chen Y, et al. Mesenchymal Stromal Cells: New Generation Treatment of Inflammatory Bowel Disease. J Inflamm Res. 2024;17:3307-3334. doi: 10.2147/JIR.S458103.

25. Zeng L, Liu C, Wu Y, Liu S, Zheng Y, Hao W, et al. Efficacy and safety of mesenchymal stromal cell transplantation in the treatment of autoimmune and rheumatic immune diseases: a systematic review and meta-analysis of randomized controlled trials. Stem Cell Res Ther. 2025;16(1):65. doi: 10.1186/s13287-025-04184-x.

26. Shaban SF, Abdel-Fattah EA, Ali MM, Dessouky AA. The therapeutic efficacy of adipose mesenchymal stem cell-derived microvesicles versus infliximab in a dextran sodium sulfate induced ulcerative colitis rat model. Ultrastruct Pathol. 2024.1-24. doi: 10.1080/01913123.2024.2426566.

DIABETES MELLITUS

Type 1 diabetes mellitus (T1DM) arises from a complex interaction between pancreatic β-cells (responsible for insulin production) and the immune system, ultimately leading to their autoimmune destruction (1). On the other hand, energy imbalance associated with overweight and obesity triggers a metabolic disorder characterized by hyperglycemia, inflammation, β-cell dysfunction, and insulin resistance, eventually progressing to the metabolic syndrome known as ***type 2 diabetes mellitus*** (T2DM) (2).

The differentiation potential of stem cells, their anti-inflammatory and immunoregulatory properties, angiogenic capacity, and positive impact on carbohydrate and lipid metabolism (3-5), have drawn significant interest from researchers and clinicians, triggering a surge in preclinical and clinical studies. These investigations aim to evaluate the safety and efficacy of stem cells and their extracellular vesicles in treating T1DM and T2DM, while also defining their mechanisms of action, optimal sources, dosages, administration routes, and dosing intervals. As a result, a substantial body of scientific evidence now supports stem cell/exosome therapy as a safe and cost-effective treatment option for diabetes mellitus.

Numerous individual studies, systematic reviews, and meta-analyses of randomized controlled clinical trials, involving hundreds of patients, confirm the safety and efficacy of stem cells/exosomes in treating both T1DM and T2DM. These therapies have demonstrated clinical and quality-of-life improvements, including better glycemic control, reduced glycated hemoglobin levels, decreased daily insulin requirements, and increased C-peptide levels. Additionally, they contribute to lowering the risk of chronic complications such as nephropathy, retinopathy, neuropathy, peripheral ischemia, and diabetic foot, among others (6-31). Furthermore, the generation of β-cells from engineered and enhanced stem cells is emerging as a promising curative approach for T1DM (32-34). Notably, baseline C-peptide concentrations serve as predictors of clinical outcomes in disease-modifying therapies like regenerative medicine (35,36).

REFERENCIAS

1. Lakey JRT, Wang Y, Alexander M, Chan MKS, Wong MBF, Casazza K, Jenkins I. Exosomes; a Potential Source of Biomarkers, Therapy, and Cure for Type-1 Diabetes. Int J Mol Sci. 2023;24(21):15713. doi: 10.3390/ijms242115713.

2. Singh A, Shadangi S, Gupta PK, Rana S. Type 2 Diabetes Mellitus: A Comprehensive Review of Pathophysiology, Comorbidities, and Emerging Therapies. Compr Physiol. 2025;15(1):e70003. doi: 10.1002/cph4.70003.

3. Esquivel D, Mishra R, Srivastava A. Mesenchymal stem cell therapy for treating the underlying causes of diabetes mellitus and its consequences. Curr Stem Cell Res Ther. 2023. doi: 10.2174/1574888X18666230411111320.

4. Tajali R, Eidi A, Tafti HA, Pazouki A, Kamarul T, Sharifi AM. Transplantation of adipose derived stem cells in diabetes mellitus; limitations and achievements. J Diabetes Metab Disord. 2023;22(2):1039-1052. doi: 10.1007/s40200-023-01280-8.

5. Yan D, Song Y, Zhang B, Cao G, Zhou H, Li H, et al. Progress and application of adipose-derived stem cells in the treatment of diabetes and its complications. Stem Cell Res Ther. 2024;15(1):3. doi: 10.1186/s13287-023-03620-0.

6. Carlsson PO, Espes D, Sisay S, Davies LC, Smith CIE, Svahn MG. Umbilical cord-derived mesenchymal stromal cells preserve endogenous insulin production in type 1 diabetes: a Phase I/II randomised double-blind placebo-controlled trial. Diabetologia. 2023. doi: 10.1007/s00125-023-05934-3.

7. Singh A, Afshan N, Singh A, Singh SK, Yadav S, Kumar M, et al. Recent trends and advances in type 1 diabetes therapeutics: A comprehensive review. Eur J Cell Biol. 2023;102(2):151329. doi: 10.1016/j.ejcb.2023.151329.

8. Al Madhoun A, Koti L, Carrió N, Atari M, Al-Mulla F. Clinical Application of Umbilical Cord Mesenchymal Stem Cells Preserves β-cells in Type 1 Diabetes. Stem Cells Transl Med. 2023:szad077. doi: 10.1093/stcltm/szad077.

9. Lian XF, Lu DH, Liu HL, Liu YJ, Yang Y, Lin Y, et al. Safety evaluation of human umbilical cord-mesenchymal stem cells in type 2 diabetes mellitus treatment: A phase 2 clinical trial. World J Clin Cases. 2023;11(21):5083-5096. doi: 10.12998/wjcc.v11.i21.5083.

10. Arango-Rodríguez ML, Mateus LC, Sossa CL, Becerra-Bayona SM, Solarte-David VA, Ochoa Vera ME, et al. A novel therapeutic management for diabetes patients with chronic limb-threatening ischemia: comparison of autologous bone marrow mononuclear cells versus allogenic Wharton jelly-derived mesenchymal stem cells. Stem Cell Res Ther. 2023;14(1):221. doi: 10.1186/s13287-023-03427-z.

11. Zang L, Li Y, Hao H, Liu J, Zhang Q, Gao F, et al. Efficacy of umbilical cord-derived mesenchymal stem cells in the treatment of type 2 diabetes assessed by retrospective continuous glucose monitoring. Stem Cells Transl Med. 2023:szad060. doi: 10.1093/stcltm/szad060.

12. Li L, Li J, Guan H, Oishi H, Takahashi S, Zhang C. Human umbilical cord mesenchymal stem cells in diabetes mellitus and its complications: applications and research advances. Int J Med Sci. 2023;20(11):1492-1507. doi: 10.7150/ijms.87472.

13. Liu J, Wan XX, Zheng SY, He HH, Khan MA, Feng YX, et al. Mesenchymal Stem Cell Transplantation in Type 1 Diabetes Treatment: Current Advances and Future Opportunity. Curr Stem Cell Res Ther. 2023. doi: 10.2174/011574888X268740231002054459.

14. Goyal P, Malviya R. Stem Cell Therapy for the Management of Type 1 Diabetes: Advances and Perspectives. Endocr Metab Immune Disord Drug Targets. 2023. doi: 10.2174/0118715303256582230919093535.

15. Habiba UE, Khan N, Greene DL, Ahmad K, Shamim S, Umer A. Meta-analysis shows that mesenchymal stem cell therapy can be a possible treatment for diabetes. Front Endocrinol (Lausanne). 2024;15:1380443. doi: 10.3389/fendo.2024.1380443.

16. Raoufinia R, Rahimi HR, Saburi E, Moghbeli M. Advances and challenges of the cell-based therapies among diabetic patients. J Transl Med. 2024;22(1):435. doi: 10.1186/s12967-024-05226-3.

17. Liu J, Yang Y, Qi Y. Efficacy of mesenchymal stromal cells in the treatment of type 1 diabetes: a systematic review. Cell Tissue Bank. 2024. doi: 10.1007/s10561-024-10128-1.

18. Leão IS, Dantas JR, Araújo DB, Ramos MEN, Silva KR, Batista LS, et al. Evaluation of type 1 diabetes' partial clinical remission after three years of heterologous adipose tissue derived stromal/stem cells transplantation associated with vitamin D supplementation. Diabetol Metab Syndr. 2024;16(1):114. doi: 10.1186/s13098-024-01302-2.

19. Memarpour S, Raoufinia R, Saburi E, Razavi MS, Attaran M, Fakoor F, Rahimi HR. The future of diabetic wound healing: unveiling the potential of mesenchymal stem cell and exosomes therapy. Am J Stem Cells. 2024;13(2):87-100. doi: 10.62347/OVBK9820.

20. Bahal M, Pande V, Dua J, Mane S. Advances in Type 1 Diabetes Mellitus Management in Children. Cureus. 2024;16(8):e67377. doi: 10.7759/cureus.67377.

21. Hetta HF, Elsaghir A, Sijercic VC, Akhtar MS, Gad SA, Moses A, et al. Mesenchymal stem cell therapy in diabetic foot ulcer: An updated comprehensive review. Health Sci Rep. 2024;7(4):e2036. doi: 10.1002/hsr2.2036.

22. Li N, Hu L, Li J, Ye Y, Bao Z, Xu Z, Chen D, Tang J, Gu Y. The Immunomodulatory effect of exosomes in diabetes: a novel and attractive therapeutic tool in diabetes therapy. Front Immunol. 2024;15:1357378. doi: 10.3389/fimmu.2024.1357378.

23. Wu Z, Huang S, Li S, Cai J, Huang L, Wu W, et al. Bone marrow mesenchymal stem cell and mononuclear cell combination therapy in patients with type 2 diabetes mellitus: a randomized controlled study with 8-year follow-up. Stem Cell Res Ther. 2024;15(1):339. doi: 10.1186/s13287-024-03907-w.

24. Ning X, Munir KM, Davis SN. Drugs stimulating insulin secretion in early clinical development for the treatment of type 1 diabetes: what's new? Expert Opin Investig Drugs. 2024. doi: 10.1080/13543784.2024.2439501.

25. Nada AH, Ibrahim IA, Oteri V, Shalabi L, Asar NK, Aqeilan SR, Hafez W. Safety and efficacy of umbilical cord mesenchymal stem cells in the treatment of type 1 and type 2 diabetes mellitus: a systematic review and meta-analysis. Expert Rev Endocrinol Metab. 2025:1-11. doi: 10.1080/17446651.2025.2457474.

26. Kim JE, Lee JW, Cha GD, Yoon JK. The Potential of Mesenchymal Stem Cell-Derived Exosomes to Treat Diabetes Mellitus. Biomimetics (Basel). 2025;10(1):49. doi: 10.3390/biomimetics10010049.

27. Lu J, Cheng H, Chen K, Zhang F. From bench to bedside: future prospects in stem cell therapy for diabetes. J Transl Med. 2025;23(1):72. doi: 10.1186/s12967-024-06019-4.

28. Abbott A. Stem cells head to the clinic: treatments for cancer, diabetes and Parkinson's disease could soon be here. Nature. 2025;637(8044):18-20. doi: 10.1038/d41586-024-04160-0.

29. Tajabadi Z, Dadkhah PA, Gholami Chahkand MS, Esmaeilpour Moallem F, Karimi MA, Amini-Salehi E, Karimi M. Exploring the role of exosomes in diabetic neuropathy: From molecular mechanisms to therapeutic potential. Biomed Pharmacother. 2025;185:117959. doi: 10.1016/j.biopha.2025.117959.

30. Tong L, Tang L, Tang B, Zhang J. Impacts of stem cells from different sources on wound healing rate in diabetic foot ulcers: a systematic review and meta-analysis. Front Genet. 2025;15:1541992. doi: 10.3389/fgene.2024.1541992.

31. Elainein MAA, Whdan MM, Samir M, Hamam NG, Mansour M, Mohamed MAM, et al. Therapeutic potential of adipose-derived stem cells for diabetic foot ulcers: a systematic review and meta-analysis. Diabetol Metab Syndr. 2025;17(1):9. doi: 10.1186/s13098-024-01523-5.

32. Fujikura J, Anazawa T, Toyoda T, Ito R, Kimura Y, Yabe D. Toward a cure for diabetes: iPSC and ESC-derived islet cell transplantation trials. J Diabetes Investig. 2024. doi: 10.1111/jdi.14366.

33. O'Leary K. Stem cells reverse type 1 diabetes. Nat Med. 2024;30(12):3393. doi: 10.1038/s41591-024-03394-9.

34. Schaaf C, Sussel L. A Cure for Type 1 Diabetes: Are We There Yet? Diabetes Technol Ther. 2025. doi: 10.1089/dia.2024.0498.

35. Wang Y, Chen H, Li Y, Hao H, Liu J, Chen Y, et al. Predictive factors that influence the clinical efficacy of umbilical cord-derived mesenchymal stromal cells in the treatment of type 2 diabetes mellitus. Cytotherapy. 2024:S1465-3249(24)00002-1. doi: 10.1016/j.jcyt.2023.12.006.

36. Latres E, Greenbaum CJ, Oyaski ML, Dayan CM, Colhoun HM, Lachin JM, et al. Evidence for C-peptide as a Validated Surrogate to Predict Clinical Benefits in Trials of Disease-Modifying Therapies for Type 1 Diabetes. Diabetes. 2024:dbi230012. doi: 10.2337/dbi23-0012.

RENAL FAILURE

Apart from renal transplantation, no available treatment for chronic renal failure can reverse disease progression; current management strategies focus solely on slowing its progression and controlling comorbidities such as hypertension, electrolyte imbalances, and anemia. Under these circumstances, the development of new therapeutic strategies aimed at restoring renal function is imperative (1,2).

The key pathological phenomenon in renal failure is inflammation and remodeling, a process in which normal structures are replaced by fibrotic tissue and blood vessel destruction, ultimately leading to the loss of renal function. Stem cells represent a promising therapeutic option for renal disease due to their regenerative properties and paracrine mechanisms, which regulate the immune response, prevent renal cell death, mitigate oxidative stress, and promote the formation of new blood vessels (3-6).

The nephroprotective effects of stem cells, by promoting regeneration and improving renal function, have been recognized in both ***acute kidney injury*** (AKI) and ***chronic kidney failure*** (CKD) of unknown origin or secondary to conditions such as diabetes, lupus, and nephrotic syndrome. In these cases, the benefits appear to be greater when stem cell therapy is combined with established treatments (1,2,5,7-15).

REFERENCES

1. Ohtake T, Sato T, Tsukiyama T, Muraoka S, Mitomo A, Maruyama H, et sl. Preliminary evidence of renal function improvement in chronic progressive kidney disease using autologous CD34⁺ cell therapy: A clinical trial. World J Stem Cells. 2024;16(12):1012-1021. doi: 10.4252/wjsc.v16.i12.1012.

2. Cheng J, Zhang C. Mesenchymal Stem Cell Therapy: Therapeutic Opportunities and Challenges for Diabetic Kidney Disease. Int J Mol Sci. 2024;25(19):10540. doi: 10.3390/ijms251910540.

3. Chen F, Chen N, Xia C, Wang H, Shao L, Zhou C, Wang J. Mesenchymal Stem Cell Therapy in Kidney Diseases: Potential and Challenges. Cell Transplant. 2023;32:9636897231164251. doi: 10.1177/09636897231164251.

4. Wang Y, Luo P, Wuren T. Narrative Review of Mesenchymal Stem Cell Therapy in Renal Diseases: Mechanisms, Clinical Applications, and Future Directions. Stem Cells Int. 2024;2024:8658246. doi: 10.1155/sci/8658246.

5. Rajput S, Malviya R, Uniyal P. Advances in the Treatment of Kidney Disorders using Mesenchymal Stem Cells. Curr Pharm Des. 2024. doi: 10.2174/0113816128296105240305110312.

6. Li J, Wu M, He L. Immunomodulatory effects of mesenchymal stem cell therapy in chronic kidney disease: a literature review. BMC Nephrol. 2025;26(1):107. doi: 10.1186/s12882-025-04029-y.

7. Carstens MH, García N, Mandayam S, Workeneh B, Pastora I, Calderón C, et al. Safety of Stromal Vascular Fraction Cell Therapy for Chronic Kidney Disease of Unknown Cause (Mesoamerican Nephropathy). Stem Cells Transl Med. 2022:szac080. doi: 10.1093/stcltm/szac080.

8. Li J, Luo M, Li B, Lou Y, Zhu Y, Bai X, et al. Immunomodulatory Activity of Mesenchymal Stem Cells in Lupus Nephritis: Advances and Applications. Front Immunol. 2022;13:843192. doi: 10.3389/fimmu.2022.843192.

9. Morello W, Budelli S, Bernstein DA, Montemurro T, Montelatici E, Lavazza C, et al. First clinical application of cord blood mesenchymal stromal cells in children with multi-drug resistant nephrotic syndrome. Stem Cell Res Ther. 2022;13(1):420. doi: 10.1186/s13287-022-03112-7.

10. Hu Q, Chen Y, Deng X, Li Y, Ma X, Zeng J, et al. Diabetic nephropathy: Focusing on pathological signals, clinical treatment, and dietary regulation. Biomed Pharmacother. 2023;159:114252. doi: 10.1016/j.biopha.2023.114252.

11. Perico N, Remuzzi G, Griffin MD, Cockwell P, Maxwell AP, Casiraghi F, et al. Safety and Preliminary Efficacy of Mesenchymal Stromal Cell (ORBCEL-M Cell) Therapy in Diabetic Kidney Disease: A Randomized Clinical Trial (NEPHSTROM). J Am Soc Nephrol. 2023. doi: 10.1681/ASN.0000000000000189.

12. Wang Y, Jin M, Cheng CK, Li Q. Tubular injury in diabetic kidney disease: molecular mechanisms and potential therapeutic perspectives. Front Endocrinol (Lausanne). 2023;14:1238927. doi: 10.3389/fendo.2023.1238927.

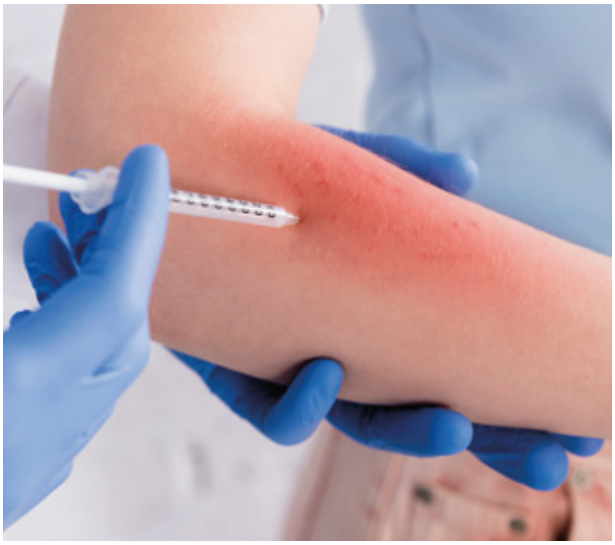
13. Salybekov AA, Kinzhebay A, Kobayashi S. Cell therapy in kidney diseases: advancing treatments for renal regeneration. Front Cell Dev Biol. 2024;12:1505601. doi: 10.3389/fcell.2024.1505601.

14. Raleigh MJ, Pasricha SV, Nauth A, Ward MR, Connelly KA. Endothelial progenitor cells for diabetic cardiac and kidney disease. Stem Cells Transl Med. 2024:szae025. doi: 10.1093/stcltm/szae025.

15. Li S, Zhou L, Huang Y, Tang S. Emerging Frontiers in acute kidney injury: The role of extracellular vesicles. Bioact Mater. 2025;48:149-170. doi: 10.1016/j.bioactmat.2025.02.018.

GRAFT-VERSUS-HOST DISEASE

Hematopoietic stem cell transplantation, derived from bone marrow, peripheral blood, or cord blood, is indicated for the treatment of leukemia, lymphomas, certain anemias, and immune disorders. The increased prevalence of these diseases in elderly individuals is primarily attributed to aging and the dysfunction of their hematopoietic stem cells (1).



However, post-transplant mortality rates remain high, mainly due to disease recurrence, infections, and graft-versus-host disease (GVHD), a consequence of a complex immune response, that can manifest in both acute and chronic forms. Although immunosuppressive drugs can help reduce its incidence, it remains high, for instance, the acute form affects between 40% and 80% of transplant patients, highlighting the urgent need for novel therapeutic approaches.

Given their potent anti-inflammatory and immunomodulatory properties, mesenchymal stem cell transplantation (e.g., from Wharton's jelly) has been investigated as a potential treatment for GVHD. While further evidence from controlled clinical trials is needed and management protocols require standarization (2), numerous studies have reported the beneficial effects of stem cells in both the prophylaxis and treatment of acute and chronic GVHD in pediatric and adult patients. Whether used alone or in combination with other immunosuppressants, stem cell therapy has been associated with improved survival. Importantly, its benefits also extend to patients with steroid-resistant GVHD (3-11).

REFERENCES

1. Colom Díaz PA, Mistry JJ, Trowbridge JJ. Hematopoietic Stem Cell Aging and Leukemia Transformation. Blood. 2023. doi: 10.1182/blood.2022017933.

2. Alsultan A, Farge D, Kili S, Forte M, Weiss DJ, Grignon F, Boelens JJ. International Society for Cell and Gene Therapy Clinical Translation Committee recommendations on mesenchymal stromal cells in graft-versus-host disease: easy manufacturing is faced with standardizing and commercialization challenges. Cytotherapy. 2024:S1465-3249(24)00713-8. doi: 10.1016/j.jcyt.2024.05.007.

3. Keklik M, Deveci B, Celik S, Deniz K, Gonen ZB, Zararsiz G, et al. Safety and efficacy of mesenchymal stromal cell therapy for multi-drug-resistant acute and late-acute graft-versus-host disease following allogeneic hematopoietic stem cell transplantation. Ann Hematol. 2023. doi: 10.1007/s00277-023-05216-3.

4. Kubota H, Arakawa Y, Mizushima Y, Irikura T, Watakabe M, Ishikawa T, et al. Efficacy of off-the-shelf bone marrow mesenchymal stem cells for pediatric steroid-refractory acute graft-versus-host disease. Blood Cell Ther. 2023;7(1):1-9. doi: 10.31547/bct-2023-020.

5. Donadel CD, Pires BG, André NC, Costa TCM, Orellana MD, Caruso SR, et al. Umbilical Cord Mesenchymal Stromal Cells for Steroid-Refractory Acute Graft-versus-Host Disease. Pharmaceuticals (Basel). 2023;16(4):512. doi: 10.3390/ph16040512.

6. Ding Y, Liu C, Cai Y, Hou C, Chen G, Xu Y, et al. The efficiency of human umbilical cord mesenchymal stem cells as a salvage treatment for steroid-refractory acute graft-versus-host disease. Clin Exp Med. 2023. doi: 10.1007/s10238-022-00983-1.

7. Ulu BU, Hindilerden IY, Yigenoglu TN, Tiryaki TO, Erkurt MA, Korkmaz G, et al. Are mesenchymal stem cells still effective in acute GvHD management? Transfus Apher Sci. 2024;64(1):104051. doi: 10.1016/j.transci.2024.104051.

8. Niu JW, Li Y, Xu C, Sheng H, Tian C, Ning H, et al. Human umbilical cord-derived mesenchymal stromal cells for the treatment of steroid refractory grades III-IV acute graft-versus-host disease with long-term follow-up. Front Immunol. 2024;15:1436653. doi: 10.3389/fimmu.2024.1436653.

9. Kim N, Min GJ, Im KI, Nam YS, Song Y, Lee JS, et al. Repeated Infusions of Bone-Marrow-Derived Mesenchymal Stem Cells over 8 Weeks for Steroid-Refractory Chronic Graft-versus-Host Disease: A Prospective, Phase I/II Clinical Study. Int J Mol Sci. 2024;25(12):6731. doi: 10.3390/ijms25126731.

10. Fu H, Sun X, Lin R, Wang Y, Xuan L, Yao H, et al. Mesenchymal stromal cells plus basiliximab improve the response of steroid-refractory acute graft-versus-host disease as a second-line therapy: a multicentre, randomized, controlled trial. BMC Med. 2024;22(1):85. doi: 10.1186/s12916-024-03275-5.

11. Peltier D, Anh Do-Thi V, Devos T, Blazar BR, Toubai T. Cellular therapies for the prevention and treatment of acute graft-versus-host disease. Stem Cells. 2025 Mar 21:sxaf009. doi: 10.1093/stmcls/sxaf009.

AUTOIMMUNE AND ALLERGIC DISEASES

After the immunomodulatory and anti-inflammatory activity of stem cells was demonstrated in *in vitro* and preclinical studies, researchers began exploring their role in various autoimmune diseases in humans, all of which are characterized by the loss of immune tolerance to self-tissues. The immunomodulatory mechanisms of stem cells and exosomes include: a) inducing the differentiation of pro-inflammatory T lymphocytes into regulatory T lymphocytes; b) inhibiting the proliferation of B lymphocytes and the production of immunoglobulins; c) promoting the conversion of pro-inflammatory macrophages into anti-inflammatory macrophages; d) inhibiting neutrophil recruitment; e) preventing the maturation of pro-inflammatory dendritic cells (1-4).

In certain autoimmune diseases, the current evidence regarding the safety and efficacy of stem cell/exosome-based therapies is considered sufficiently robust for experts from various scientific societies to issue consensus recommendations, such as the following: "Cell therapy may be considered as a therapeutic option in patients with severe autoimmune diseases being active or progressing despite the use of standard (guideline-based and/or regulatory approved) therapy" ... "Depending on the half-life and efficacy of the cellular product, repeated application might be necessary, as already shown for stem cells" (5).

RHEUMATOID ARTHRITIS (RA)

30-40% of patients with rheumatoid arthritis (RA) do not respond adequately to or cannot tolerate conventional treatments; in such cases, stem cells/exosomes have emerged as a promising therapeutic option. Increasing evidence supports the benefits of stem cell/exosome-based therapies in patients with poor responses to standard treatment, including reductions in inflammation markers and clinical improvements (6-19). It has even been shown that stem cells have an enhanced effect when combined with conventional drugs like gamma-interferon (20).

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

This is one of the autoimmune diseases with the strongest evidence supporting the benefits and safety of stem cells/exosomes, both in animal models and humans (21-27). The results from clinical trials on the safety and efficacy of stem cell/exosome therapies are promising, with several positive outcomes reported, including a) improvement in clinical manifestations and damage to renal, pulmonary, hepatic, and bone tissues; b) enhancement of immune parameters, such as the conversion of pro-inflammatory lymphocytes into anti-inflammatory ones, and a reduction in autoantibody levels (including antinuclear antibodies and anti-DNA antibodies) (28); c) increased survival rates; and d) a broad safety margin. It is important to highlight that stem cell/exosome-based therapy is currently the most viable option for patients with lupus refractory to conventional treatment, including glucocorticoids (18,29-31).

SYSTEMIC SCLEROSIS (SS)

It is an autoimmune disease characterized by vascular damage, immune system dysfunction, and fibrosis of the skin and multiple organs. Treatment options are highly limited, and the medications that may be useful have a narrow safety margin. Cell therapy emerges as not only a safe option but also one capable of correcting many of the inflammatory, fibrotic, and

immune-related disorders inherent to this disease. Clinical studies and reviews have confirmed the safety and significant benefits of stem cell/exosome therapy, with some cases demonstrating superior efficacy compared to traditional immunosuppressive agents, and no increase in the incidence of adverse events, when applied to patients with systemic sclerosis (32-42).

SJÖGREN'S SYNDROME (SS)

In this disease, the immune system initially targets the patient's own salivary and lacrimal glands, resulting in dry mouth and eyes. In more severe forms, however, it can lead to chronic inflammation and dysfunction in other organs, including the lungs, kidneys, liver, and brain (43). The imbalance among different T lymphocyte populations plays a key role in the progression of the disease, and currently, no effective treatment is available (44,45).

Although clinical evidence on the risk/benefit of regenerative medicine remains limited, recent studies have demonstrated that stem cells/exosomes are effective in treating Sjögren's syndrome by modulating the immune response and promoting tissue repair (46-50). It is worth noting that stem cells/exosomes have also demonstrated benefits in other forms of xerostomia (dry mouth), such as that secondary to radiation therapy (51).

PSORIASIS

A significant number of patients with psoriasis do not respond adequately to current therapies. As an autoimmune disease, psoriasis involves the patient's stem cells in the excessive and sustained production of inflammatory substances. Given the anti-inflammatory and immunomodulatory properties of stem cells/exosomes, a positive response to stem cell therapy was anticipated. The therapeutic effect and safety of stem cells/exosomes in the treatment of psoriasis are no longer debated. Instead, expert consensus focuses on refining aspects such as the source of the cells and exosomes, dosage, administration routes (injection or topical), and other related factors. (18,52-58).

ATOPIC DERMATITIS

Stem cells/exosomes have emerged as a promising strategy for treating allergic diseases (such as asthma, rhinitis, dermatitis, conjunctivitis, and anaphylaxis) due to their immunoregulatory and anti-inflammatory properties (59). This therapeutic potential has been demonstrated through preclinical and clinical studies. However, atopic dermatitis is the allergic disease with the strongest evidence supporting the benefit and safety of stem cell/exosome treatment (60-64).

REFERENCES

1. Wang Z, Yang C, Yan S, Sun J, Zhang J, Qu Z, et al. Emerging Role and Mechanism of Mesenchymal Stem Cells-Derived Extracellular Vesicles in Rheumatic Disease. J Inflamm Res. 2024;17:6827-6846. doi: 10.2147/JIR.S488201.
2. Liao HJ, Hsu PN. Immunomodulatory effects of extracellular vesicles from mesenchymal stromal cells: Implication for therapeutic approach in autoimmune diseases. Kaohsiung J Med Sci. 2024. doi: 10.1002/kjm2.12841.
3. Li L, He Y, Zhao J, Yin H, Feng X, Fan X, et al. Mesenchymal Stromal Cell-Based Therapy: A Promising Approach for Autoimmune Diseases. Clin Rev Allergy Immunol. 2025;68(1):21. doi: 10.1007/s12016-025-09030-9.
4. Feng Z, Yang Y, Liu XZ, Sun HJ, Wen BY, Chen Z, Wei B. Application of cell therapy in rheumatoid Arthritis: Focusing on the immunomodulatory strategies of Mesenchymal stem cells. Int Immunopharmacol. 2025;147:114017. doi: 10.1016/j.intimp.2025.114017.
5. Greco R, Alexander T, Del Papa N, Müller F, Saccardi R, Sanchez-Guijo F, et al. Innovative cellular therapies for autoimmune diseases: expert-based position statement and clinical practice recommendations from the EBMT practice harmonization and guidelines committee. EClinicalMedicine. 2024;69:102476. doi: 10.1016/j.eclinm.2024.102476.
6. Shimizu Y, Ntege EH, Azuma C, Uehara F, Toma T, Higa K, et al. Management of Rheumatoid Arthritis: Possibilities and Challenges of Mesenchymal Stromal/Stem Cell-Based Therapies. Cells. 2023;12(14):1905. doi: 10.3390/cells12141905.
7. Rahimi Khorashad M, Ghoryani M, Gowhari Shabgah A, Shariati-Sarabi Z, Tavakkol Afshari J, Mohammadi M. The Effects of Mesenchymal Stem Cells on the Gene Expression of TGF-beta and IFN-gamma in Patients with Rheumatoid Arthritis. Iran J Allergy Asthma Immunol. 2023;22(2):183-189. doi: 10.18502/ijaai.v22i2.12679.
8. Moghaddam MZ, Mousavi MJ, Ghotloo S. Cell-based therapies for the treatment of rheumatoid arthritis. Immun Inflamm Dis. 2023;11(11):e1091. doi: 10.1002/iid3.1091.
9. Babaahmadi M, Tayebi B, Gholipour NM, Kamardi MT, Heidari S, Baharvand H, et

al. Rheumatoid arthritis: the old issue, the new therapeutic approach. Stem Cell Res Ther. 2023;14(1):268. doi: 10.1186/s13287-023-03473-7.
10. Qi W, Li F, Wang G, Yan Y, Tian J, Wang T, et al. The effects of mesenchymal stem cells-derived exosomes in rheumatoid arthritis: a review. Clin Exp Rheumatol. 2023. doi: 10.55563/clinexprheumatol/l49ccg.
11. Lee BW, Kwok SK. Mesenchymal Stem/Stromal Cell-Based Therapies in Systemic Rheumatic Disease: From Challenges to New Approaches for Overcoming Restrictions. Int J Mol Sci. 2023;24(12):10161. doi: 10.3390/ijms241210161.
12. Bakinowska E, Kiełbowski K, Pawlik A. The Role of Extracellular Vesicles in the Pathogenesis and Treatment of Rheumatoid Arthritis and Osteoarthritis. Cells. 2023;12(23):2716. doi: 10.3390/cells12232716.
13. Abebaw D, Akelew Y, Adugna A, Teffera ZH, Tegegne BA, Fenta A, et al. Extracellular vesicles: immunomodulation, diagnosis, and promising therapeutic roles for rheumatoid arthritis. Front Immunol. 2024;15:1499929. doi: 10.3389/fimmu.2024.1499929.
14. Bakinowska E, Bratborska AW, Kiełbowski K, Ćmil M, Biniek WJ, Pawlik A. The Role of Mesenchymal Stromal Cells in the Treatment of Rheumatoid Arthritis. Cells. 2024;13(11):915. doi: 10.3390/cells13110915.
15. Li C, Sun Y, Xu W, Chang F, Wang Y, Ding J. Mesenchymal Stem Cells-Involved Strategies for Rheumatoid Arthritis Therapy. Adv Sci (Weinh). 2024:e2305116. doi: 10.1002/advs.202305116.
16. Pignatti E, Maccaferri M, Pisciotta A, Carnevale G, Salvarani C. A comprehensive review on the role of mesenchymal stromal/stem cells in the management of rheumatoid arthritis. Expert Rev Clin Immunol. 2024:1-23. doi: 10.1080/1744666X.2023.2299729.
17. Chasov V, Ganeeva I, Zmievskaya E, Davletshin D, Gilyazova E, Valiullina A, Bulatov E. Cell-Based Therapy and Genome Editing as Emerging Therapeutic Approaches to Treat Rheumatoid Arthritis. Cells. 2024;13(15):1282. doi: 10.3390/cells13151282.
18. Fu Y, Feng C, Qin S, Xing Z, Liu C, Liu Z, Yu H. Breaking barriers: advancing cellular therapies in autoimmune disease management. Front Immunol. 2024;15:1503099. doi: 10.3389/fimmu.2024.1503099.
19. Miao X, Ghafourian A, Karimi Khaneghah M, Ayyoubzadeh SM, Afrisham R, Ahmadi M. Extracellular vesicles as therapeutic agents in rheumatoid arthritis: a systematic review of current evidence. Inflammopharmacology. 2025. doi: 10.1007/s10787-025-01670-9.
20. Nie DQ, Yan GX, Wang ZY, Yan X, Yu GM, Gao JL, et al. Combination treatment with interferon-γ may be a potential strategy to improve the efficacy of cytotherapy for rheumatoid arthritis: A network meta-analysis. J Res Med Sci. 2024;29:29. doi: 10.4103/jrms.jrms_697_21.
21. Barbado J. Mesenchymal stem cell transplantation may be able to induce immunological tolerance in systemic lupus erythematosus. Biomed J. 2024:100724. doi: 10.1016/j.bj.2024.100724.
22. Dao LTM, Vu TT, Nguyen QT, Hoang VT, Nguyen TL. Current cell therapies for systemic lupus erythematosus. Stem Cells Transl Med. 2024:szae044. doi: 10.1093/stcltm/szae044.
23. Yordanova A, Ivanova M, Tumangelova-Yuzeir K, Angelov A, Kyurkchiev S, Belemezova K, et al. Umbilical Cord Mesenchymal Stem Cell Secretome: A Potential Regulator of B Cells in Systemic Lupus Erythematosus. Int J Mol Sci. 2024;25(23):12515. doi: 10.3390/ijms252312515.
24. Wisnu Prajoko Y, Putra A, Prasetio A, Dina Amalina N. Hypoxic mesenchymal stem cells (MSCS)-induced interleukin (IL)-10 alleviate systemic lupus erythematosus (SLE) infl ammation through inhibiting interferon (IFN)-gamma production. Med Glas (Zenica). 2024;21(1):1-7. doi: 10.17392/1608-23.
25. Rajeev Kumar S, Sakthiswary R, Lokanathan Y. Potential Therapeutic Application and Mechanism of Action of Stem Cell-Derived Extracellular Vesicles (EVs) in Systemic Lupus Erythematosus (SLE). Int J Mol Sci. 2024;25(4):2444. doi: 10.3390/ijms25042444.
26. Ginting AR, Munir D, Amin MM, Darlan DM, Putra A, Rusda M, et al. Mesenchymal stem cells for immune modulation in systemic lupus erythematosus: From bench research to clinical applications. Narra J. 2024;4(3):e994. doi: 10.52225/narra.v4i3.994.
27. Ding M, Jin L, Cui S, Yang L, He J, Wang X, et al. Human Umbilical Cord Mesenchymal Stem Cells for the Treatment of Systemic Lupus Erythematosus via Glucose Metabolism of CD4+T Cells. Stem Cell Rev Rep. 2025. doi: 10.1007/s12015-025-10848-1.
28. Zhang YH, Chen J, Mao WF, Yan LX, Long F, Li SH, Zhang RX. Harnessing miR-16-5p-Loaded Exosomes from Adipose-Derived Stem Cells to Restore Immune Homeostasis in SLE Patients. Immunobiology. 2025;230(3):152885. doi: 10.1016/j.imbio.2025.152885.
29. Xia Y, Ye H, Li K, Shi B, Sun X, Wu J. Efficacy of Mesenchymal Stem Cell Therapy on Lupus Nephritis and Renal Function in Systemic Lupus Erythematosus: A Meta-Analysis. Clin Invest Med. 2023;46(1):E24-35. doi: 10.25011/cim.v46i1.39561.
30. Zare Moghaddam M, Mousavi MJ, Ghotloo S. Stem cell-based therapy for systemic lupus erythematous. J Transl Autoimmun. 2024;8:100241. doi: 10.1016/j.jtauto.2024.100241.
31. Athanassiou P, Athanassiou L, Kostoglou-Athanassiou I, Shoenfeld Y. Targeted Cellular Treatment of Systemic Lupus Erythematosus. Cells. 2025;14(3):210. doi: 10.3390/cells14030210.
32. Laranjeira P, Dos Santos F, Salvador MJ, Simões IN, Cardoso CMP, Silva BM, et al. Umbilical-Cord-Derived Mesenchymal Stromal Cells Modulate 26 Out of 41 T Cell Subsets from Systemic Sclerosis Patients. Biomedicines. 2023;11(5):1329. doi: 10.3390/biomedicines11051329.
33. Zhao K, Kong C, Shi N, Jiang J, Li P. Potential angiogenic, immunomodulatory, and antifibrotic effects of mesenchymal stem cell-derived extracellular vesicles in systemic sclerosis. Front Immunol. 2023;14:1125257. doi: 10.3389/fimmu.2023.1125257.
34. Zeng L, Yang K, Yu G, Chen J, Long Z, Xiang W, et al. Efficacy and safety of culture-expanded mesenchymal stromal cell therapy in the treatment of 4 types of inflammatory arthritis: A systematic review and meta-analysis of 36 randomized controlled trials. Semin Arthritis Rheum. 2024;68:152498. doi: 10.1016/j.semarthrit.2024.152498.
35. Del Papa N, Cavalli S, Rindone A, Onida F, Saporiti G, Minniti A, et al. Long-term outcome of autologous haematopoietic stem cell transplantation in patients with systemic sclerosis: a comparison with patients treated with rituximab and with traditional immunosuppressive agents. Arthritis Res Ther. 2024;26(1):182. doi: 10.1186/s13075-024-03408-4.
36. Alip M, Wang D, Zhao S, Li S, Zhang D, Duan X, et al. Umbilical cord mesenchymal stem cells transplantation in patients with systemic sclerosis: a 5-year follow-up study. Clin Rheumatol. 2024. doi: 10.1007/s10067-024-06865-z.
37. Maltez N, Wang M, Wells GA, Tugwell P, Baron M, Marjanovic Z, et al. Improvement in Skin Fibrosis and Lung Function with Autologous Hematopoietic Stem Cell Transplantation in Systemic Sclerosis. Transplant Cell Ther. 2025:S2666-6367(25)01011-5. doi: 10.1016/j.jtct.2025.02.005.
38. Foeldvari I, Torok KS, Furtado E Silva J, Denton CP, Henes J, Horvei P, et al. Guidance for stem cell therapy for juvenile systemic sclerosis patients. Expert Rev Clin Immunol. 2025. doi: 10.1080/1744666X.2025.2474216.
39. Yuan W, Liu M, Yang D, Shi Y, Wang Z, Cao X, et al. Improvement in long-term survival with mesenchymal stem cell transplantation in systemic sclerosis patients: a propensity score-matched cohort study. Stem Cell Res Ther. 2025;16(1):128. doi: 10.1186/s13287-025-04237-1.
40. Napolitano F, Giudice V, D'Esposito V, Prevete N, Scala P, de Paulis A, et al. Cell-free regenerative medicine: identifying the best source of mesenchymal stem cells for skin therapy in Systemic Sclerosis. Front Cell Dev Biol. 2025;13:1518412. doi: 10.3389/fcell.2025.1518412.
41. Bautista Sanchez R, Khader Y, Khanna D. Management of cutaneous manifestations of systemic sclerosis: current approaches and emerging therapies. Curr Opin Rheumatol. 2025. doi: 10.1097/BOR.0000000000001082.
42. Chen C, Nishtala A, Li E, Schultz WM, Baldridge AS, Groenendyk JW, et al. The effect of hematopoietic stem cell transplantation on cardiac mechanics in systemic sclerosis. Int J Cardiovasc Imaging. 2025. doi: 10.1007/s10554-025-03365-2.
43. Harrell CR, Volarevic A, Arsenijevic A, Djonov V, Volarevic V. Targeted Therapy for Severe Sjogren's Syndrome: A Focus on Mesenchymal Stem Cells. Int J Mol Sci. 2024;25(24):13712. doi: 10.3390/ijms252413712.
44. Xie Y, Chai M, Xing Y, Zhou P, Wei P, Hua H. miRNA let-7f-5p-encapsulated labial gland MSC-derived EVs ameliorate experimental Sjögren's syndrome by suppressing Th17 cells via targeting RORC/IL-17A signaling axis. J Nanobiotechnology. 2025;23(1):228. doi: 10.1186/s12951-025-03308-y.
45. Ma ZX, Wu XF, Cao L, Jiao CY, Ma DP, Zhao YH, et al. Regenerative fibroblasts derived from autologous skin tissue for the treatment of Sjögren's syndrome: a case report. Front Immunol. 2025;16:1529883. doi: 10.3389/fimmu.2025.1529883.
46. Møller-Hansen M, Larsen AC, Wiencke AK, Terslev L, Siersma V, Andersen TT, et al. Allogeneic mesenchymal stem cell therapy for dry eye disease in patients with Sjögren's syndrome: A randomized clinical trial. Ocul Surf. 2024;31:1-8. doi: 10.1016/j.jtos.2023.11.007.
47. Shahsavari A, Liu F. Diagnostic and therapeutic potentials of extracellular vesicles for primary Sjögren's Syndrome: A review. Dent Rev (N Y). 2024;4(3):100150. doi: 10.1016/j.dentre.2024.100150.
48. Harrell CR, Volarevic A, Arsenijevic A, Djonov V, Volarevic V. Targeted Therapy for Severe Sjogren's Syndrome: A Focus on Mesenchymal Stem Cells. Int J Mol Sci. 2024;25(24):13712. doi: 10.3390/ijms252413712.
49. Cui X, Liu L, Duan C, Mao S, Wang G, Li H, et al. A review of the roles of exosomes in salivary gland diseases with an emphasis on primary Sjögren's syndrome. J Dent Sci. 2025;20(1):1-14. doi: 10.1016/j.jds.2024.10.001.
50. Zeng L, Liu C, Wu Y, Liu S, Zheng Y, Hao W, et al. Efficacy and safety of mesenchymal stromal cell transplantation in the treatment of autoimmune and rheumatic immune diseases: a systematic review and meta-analysis of randomized controlled trials. Stem Cell Res Ther. 2025;16(1):65. doi: 10.1186/s13287-025-04184-x.
51. Aritzi I, Konstantinidis I, Kyriakidou A, Garefis K, Sideris G, Delides A. The use of stem cells in treating xerostomia: a systematic review. Eur Arch Otorhinolaryngol. 2024. doi: 10.1007/s00405-024-08829-0.
52. Wang Z, Hu Y, Wang X, Chen Y, Wu D, Ji H, et al. Comparative Analysis of the Therapeutic Effects of Fresh and Cryopreserved Human Umbilical Cord Derived Mesenchymal Stem Cells in the Treatment of Psoriasis. Stem Cell Rev Rep. 2023. doi: 10.1007/s12015-023-10556-8.
53. Bajouri A, Dayani D, Taj Sharghi A, Karimi S, Niknezhadi M, Moeinabadi Bidgoli K, et al. Subcutaneous Injection of Allogeneic Adipose-Derived Mesenchymal Stromal Cells in Psoriasis Plaques: Clinical Trial Phase I. Cell J. 2023;25(6):363-371. doi: 10.22074/cellj.2023.1973793.1167.
54. Dairov A, Sekenova A, Alimbek S, Nurkina A, Shakhatbayev M, Kumasheva V, et al. Psoriasis: The Versatility of Mesenchymal Stem Cell and Exosome Therapies. Biomolecules. 2024;14(11):1351. doi: 10.3390/biom14111351.
55. Song M, Lim KM, Song K, Kang GH, Kim SJ, Lee Y, et al. Efficient Treatment of Psoriasis Using Conditioned Media from Mesenchymal Stem Cell Spheroids Cultured to Produce Transforming Growth Factor-β1-Enriched Small-Sized Extracellular Vesicles. Int J Stem Cells. 2024. doi: 10.15283/ijsc24089.
56. Meybodi MAM, Nilforoushzadeh MA, KhandanDezfully N, Mansouri P. The safety and efficacy of adipose tissue-derived exosomes in treating mild to moderate plaque psoriasis: A clinical study. Life Sci. 2024:122915. doi: 10.1016/j.lfs.2024.122915.
57. Kuang YH, Zhu W, Lin G, Cheng LM, Qin Q, Huang ZJ, et al. Expert Consensus on the Application of Stem Cells in Psoriasis Research and Clinical Trials. Aging Dis. 2024. doi: 10.14336/AD.2024.0012.
58. Chandran NS, Bhupendrabhai MN, Tan TT, Zhang B, Lim SK, Choo ABH, Lai RC. A phase 1, open-label study to determine safety and tolerability of the topical application of mesenchymal stem/stromal cell (MSC) exosome ointment to treat psoriasis in healthy volunteers. Cytotherapy. 2025:S1465-3249(25)00031-3. doi: 10.1016/j.jcyt.2025.01.007.
59. Peng YQ, Deng XH, Xu ZB, Wu ZC, Fu QL. Mesenchymal stromal cells and their small extracellular vesicles in allergic diseases: from immunomodulation to therapy. Eur J Immunol. 2023:e2149510. doi: 10.1002/eji.202149510.
60. Yang J, Xiao M, Ma K, Li H, Ran M, Yang S, et al. Therapeutic effects of mesenchymal stem cells and their derivatives in common skin inflammatory diseases: Atopic dermatitis and psoriasis. Front Immunol. 2023;14:1092668. doi: 10.3389/fimmu.2023.1092668.
61. Seo HM, Lew BL, Lee YW, Son SW, Park CO, Park YL, ET AL. Phase 1/2 trials of human bone marrow-derived clonal mesenchymal stem cells for treatment of adults with moderate to severe atopic dermatitis. J Allergy Clin Immunol. 2024;154(4):965-973. doi: 10.1016/j.jaci.2024.06.013.
62. He K, Zang J, Ren T, Feng S, Liu M, Zhang X, et al. Therapeutic Potential and Mechanisms of Mesenchymal Stem Cell and Mesenchymal Stem Cell-Derived Extracellular Vesicles in Atopic Dermatitis. J Inflamm Res. 2024;17:5783-5800. doi: 10.2147/JIR.S479444.
63. Dukharan V, Shah M, Broughton L, Stegura C, Samman L, Schur N, Schlesinger T. The Role of Exosomes in Medical Dermatology: Literature Review and Update. J Cosmet Dermatol. 2025;24(1):e16761. doi: 10.1111/jocd.16761.
64. Al-Masawa ME, Elfawy LA, Ng CY, Ng MH, Law JX. Mesenchymal Stromal Cell-Derived Extracellular Vesicles in the Management of Atopic Dermatitis: A Scoping Review of Therapeutic Opportunities and Challenges. Int J Nanomedicine. 2025;20:2673-2693. doi: 10.2147/IJN.S494574.

NEURODEGENERATIVE DISEASES

Several neurodegenerative diseases, including multiple sclerosis, amyotrophic lateral sclerosis, Alzheimer's disease, and Parkinson's disease, are considered incurable. Current medical treatments are primarily palliative; for instance, disease-modifying therapies can help control the progression of intermittent forms of multiple sclerosis, but none can repair existing damage. In recent years, there has been significant interest in determining the role of stem cell/exosome based therapies in various neurodegenerative diseases. *In vitro* studies and diverse animal models have confirmed several properties of different types of stem cells, including the restoration of blood-brain barrier (BBB) integrity, the formation of new myelin, the transfer of mitochondria to vulnerable neurons, the prolongation of neuronal viability, the reduction of oxidative stress, immunomodulation, and the formation of new blood vessels, all of which contribute to neuroprotection. However, for some of these diseases, further evidence is still needed regarding safety and efficacy, optimal cell types, appropriate dosing, and administration routes, among others (1–8).

MULTIPLE SCLEROSIS (MS)

It is caused by the destruction of myelin, which disrupts neuronal electrical activity and leads to a progressive loss of brain function. Regenerative medicine-based treatment has achieved a level of evidence that has led scientific organizations to recommend it for severe forms of the disease. Health authorities have also approved it in some countries. Current research is focused on refining critical aspects, including identifying the most responsive disease subtypes (particularly relapsing-remitting forms) optimizing administration routes, determining optimal dosing and intervals, and assessing interactions with conventional therapies (9–16). Compared to standard immunotherapy, stem cell/exosome treatments have been associated with disease stabilization, delayed progression, improved Expanded Disability Status Scale (EDSS) scores, reduced brain lesion volume, enhanced cognitive function, and increased life expectancy. Additionally, these benefits are accompanied by a reduction in biomarkers of disease activity in blood and cerebrospinal fluid (17-29). Moreover, when hematopoietic stem cell therapy was compared to disease-modifying treatments including "high-efficacy" drugs such as natalizumab, stem cell therapy has proven to be more effective and less expensive in patients with the aggressive relapsing-remitting form of the disease (30,31).

AMYOTROPHIC LATERAL SCLEROSIS (ALS)

EIt is a disease with genetic and non-genetic determinants, characterized by the destruction of motor neurons in the brain and spinal cord, neurovascular damage, and muscle degeneration, leading to paralysis, respiratory failure, and premature death (32). Stem cell/exosome therapy has been consolidated as a safe procedure and a promising strategy that protects motor neurons, slows the loss of motor function, reduces symptom severity, and improves survival rates (33–39).

PARKINSON'S DISEASE (PD)

More than 10 million people worldwide are believed to be affected by PD, a condition characterized by the progressive degeneration of neurons in specific areas of the brain. At the molecular level, PD is associated with the formation of abnormal aggregates of the α-synuclein and the disruption of the BBB (which regulates the entry and exit of molecules in the brain and maintains the normal functioning of the central nervous system). This disruption leads to inflammation and neuronal damage. Stem cells/exosomes help restore BBB integrity and prevent α-synuclein aggregation, resulting in reduced inflammation and neuronal toxicity (40,41).

Current treatment approaches primarily focus on symptom management through medications or neurosurgery, but they do not address the prevention of neuronal damage. Therefore, there is a critical need to develop neuroprotective strategies that offer the potential to replace lost neurons. Studies on the safety and efficacy of stem cell/exosome therapy in animal models have yielded conclusive results, making regenerative medicine a central focus of attention within the medical community. Currently, clinical evidence from trials and meta-analyses can be summarized as follows: i) safety studies in humans are unequivocal, showing that stem cells are a therapeutic tool with a very low incidence of undesirable effects and are not associated with serious adverse events; ii) evidence from efficacy studies continues to strengthen, with stem cells emerging as a promising therapy linked to improvements in patients' clinical condition and imaging findings; iii) stem cells regenerate damaged areas of the brain and provide neurotrophic support; iv) they also improve neuropsychological scores in patients (42–49). It is worth noting that, based on various experimental findings, induced pluripotent stem cells (iPSCs) demonstrate exceptional therapeutic potential in Parkinson's disease and may rapidly emerge as the leading option for regenerative treatment (50,51).

ALZHEIMER'S DISEASE (AD)

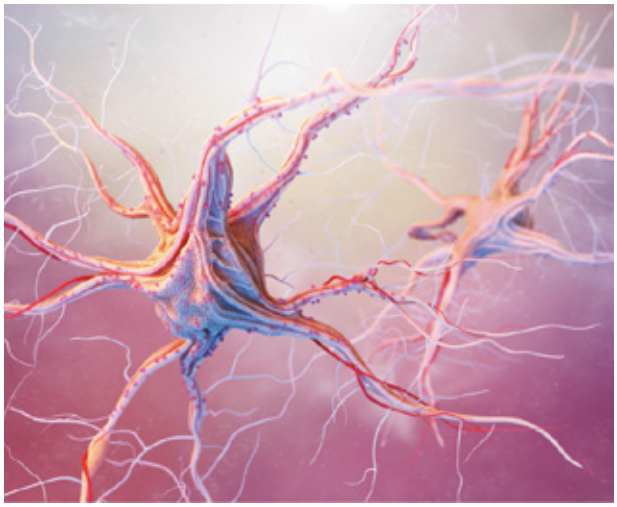
It is a highly prevalent disease and a leading cause of mortality in the elderly, characterized by cognitive decline, memory loss, disorientation, language impairments, and a reduced ability to solve problems. The accumulation of intraneuronal tau protein deposits and the formation of extraneuronal β-amyloid (Aβ) plaques are key molecular events that ultimately lead to neuroinflammation and neuronal degeneration.

Due to the complexity of this disease, the therapeutic approach to AD is inherently multimodal, integrating pharmacological and non-pharmacological components. However, the outcomes of these recommended interventions remain discouraging, as they can, at best, manage certain symptoms but do not cure the disease, repair the damage, or stop its progression. In this context, stem cells/exosomes have emerged as a promising alternative, as they have demonstrated the ability to regulate numerous biochemical signals involved in the brain damage caused by AD (52-57).

In vitro and preclinical studies have confirmed the neuroprotective and neuroregenerative effects of stem cells/exosomes in animal models of AD, including the following outcomes: a) reduction of cognitive deficits, accompanied by increased levels

of neurotrophic factors; b) memory improvement; c) promotion of neurogenesis and synaptic plasticity, the site of communication between neurons; d) inhibition of Aβ plaque deposition and enhancement of its degradation (58-60).

Although evidence in humans remains limited, the safety and efficacy results obtained so far have secured stem cells/exosomes a prominent place in the treatment of AD. This topic is under scrutiny by the scientific community, with numerous clinical trials either published or currently underway. Several authorities consider the clinical outcomes so promising that they are steadily advancing in the identification of biomarkers to predict and/or monitor the response to this regenerative therapy (61-68).



EPILEPSY

It is an electrical disorder of the brain, characterized by recurrent convulsive seizures that progressively damage neurons. Approximately 70% of patients respond favorably to existing anti-epileptic agents, while up to 30% remain refractory to pharmacological therapy, which is associated with significant adverse effects. In these circumstances, the pursuit of new therapeutic options remains a top priority in neuroscience research.

As the anti-inflammatory, antioxidant, immunomodulatory, and neuroprotective effects of stem cells have been increasingly confirmed, evidence of their safety and efficacy has also been strengthened in preclinical and clinical studies, including drug-resistant forms of epilepsy. Stem cells have been associated with a reduction in the frequency, intensity, and duration of seizures, as well as the management of certain neuropsychiatric disorders that often result from this condition (69-72).

REFERENCES

1. Jayaprakash B, Savira M, Mahmood AAR, Prasanna M. The Role of Stem Cell Therapies in the Treatment of Neurodegenerative Diseases. Curr Stem Cell Res Ther. 2024. doi: 10.2174/011574888X313112240510160102.
2. Khandia R, Gurjar P, Priyanka, Romashchenko V, Al-Hussain SA, Zaki MEA. Recent advances in stem cell therapy: efficacy, ethics, safety concerns, and future directions focusing on neurodegenerative disorders - a review. Int J Surg. 2024;110(10):6367-6381. doi: 10.1097/JS9.0000000000001609.
3. Bruno A, Milillo C, Anaclerio F, Buccolini C, Dell'Elice A, Angilletta I, Gatta M, Ballerini P, Antonucci I. Perinatal Tissue-Derived Stem Cells: An Emerging Therapeutic Strategy for Challenging Neurodegenerative Diseases. Int J Mol Sci. 2024;25(2):976. doi: 10.3390/ijms25020976.
4. Manora L, Borlongan CV, Garbuzova-Davis S. Cellular and Noncellular Approaches for Repairing the Damaged Blood-CNS-Barrier in Amyotrophic Lateral Sclerosis. Cells. 2024;13(5):435. doi: 10.3390/cells13050435.
5. Zhang X, Che X, Zhang S, Wang R, Li M, Jin Y, et al. Mesenchymal stem cell-derived extracellular vesicles for human diseases. Extracell Vesicles Circ Nucl Acids. 2024;5(1):64-82. doi: 10.20517/evcna.2023.47.
6. Dadfar S, Yazdanpanah E, Pazoki A, Nemati MH, Eslami M, Haghmorad D, Oksenych V. The Role of Mesenchymal Stem Cells in Modulating Adaptive Immune Responses in Multiple Sclerosis. Cells. 2024;13(18):1556. doi: 10.3390/cells13181556.
7. Izrael M, Chebath J, Molakandov K, Revel M. Clinical perspective on pluripotent stem cells derived cell therapies for the treatment of neurodegenerative diseases. Adv Drug Deliv Rev. 2025:115525. doi: 10.1016/j.addr.2025.115525.
8. Sun B, Li L, Harris OA, Luo J. Blood-brain barrier disruption: a pervasive driver and mechanistic link between traumatic brain injury and Alzheimer's disease. Transl Neurodegener. 2025;14(1):16. doi: 10.1186/s40035-025-00478-5.
9. Jespersen F, Petersen SL, Andersen P, Sellebjerg F, Magyari M, Sørensen PS, Blinkenberg M. Autologous hematopoietic stem cell transplantation of patients with aggressive relapsing-remitting multiple sclerosis: Danish nation-wide experience. Mult Scler Relat Disord. 2023;76:104829. doi: 10.1016/j.msard.2023.104829.
10. Wu L, Lu J, Lan T, Zhang D, Xu H, Kang Z, et al. Stem cell therapies: a new era in the treatment of multiple sclerosis. Front Neurol. 2024;15:1389697. doi: 10.3389/fneur.2024.1389697.
11. Ghareghani M, Arneaud A, Rivest S. The evolution of mesenchymal stem cell-derived neural progenitor therapy for Multiple Sclerosis: from concept to clinic. Front Cell Neurosci. 2024;18:1428652. doi: 10.3389/fncel.2024.1428652.
12. Rashid W, Ciccarelli O, Leary SM, Arun T, Doshi A, Evangelou N, et al; Association Of British Neurologists Multiple Sclerosis and Neuroinflammation Advisory Group. Using disease-modifying treatments in multiple sclerosis: Association of British Neurologists (ABN) 2024 guidance. Pract Neurol. 2024:pn-2024-004228. doi: 10.1136/pn-2024-004228.
13. Braun B, Fischbach F, Pfeffer LK, Richter J, Janson D, Kröger NM, et al. Exploring the therapeutic potential of autologous hematopoietic stem cell transplantation in progressive multiple sclerosis-a systematic review. Eur J Neurol. 2024;31(12):e16427. doi: 10.1111/ene.16427.
14. Burt RK, Alexander T; EBMT Autoimmune Diseases Working Party (ADWP). Hematopoietic stem cell transplantation for multiple sclerosis: no inflammation, no response. Eur J Neurol. 2025;32(1):e16565. doi: 10.1111/ene.16565.
15. Sheikhi K, Ghaderi S, Firouzi H, Rahimibarghani S, Shabani E, Afkhami H, et al. Recent advances in mesenchymal stem cell therapy for multiple sclerosis: clinical applications and challenges. Front Cell Dev Biol. 2025;13:1517369. doi: 10.3389/fcell.2025.1517369.
16. Muraro PA, Mariottini A, Greco R, Burman J, Iacobaeus E, Inglese M, et al. Autologous haematopoietic stem cell transplantation for treatment of multiple sclerosis and neuromyelitis optica spectrum disorder - recommendations from ECTRIMS and the EBMT. Nat Rev Neurol. 2025. doi: 10.1038/s41582-024-01050-x.
17. Islam MA, Alam SS, Kundu S, Ahmed S, Sultana S, Patar A, Hossan T. Mesenchymal Stem Cell Therapy in Multiple Sclerosis: A Systematic Review and Meta-Analysis. J Clin Med. 2023;12(19):6311. doi: 10.3390/jcm12196311.
18. Msheik A, Assi F, Hamed F, Jibbawi A, Nakhl AM, Khoury A, et al. Stem Cell Transplantation for Multiple Sclerosis: A 2023 Review of Published Studies. Cureus. 2023;15(10):e47972. doi: 10.7759/cureus.47972.
19. Hijal N, Fouani M, Awada B. Unveiling the fate and potential neuroprotective role of neural stem/progenitor cells in multiple sclerosis. Front Neurol. 2024;15:1438404. doi: 10.3389/fneur.2024.1438404.
20. Vaheb S, Afshin S, Ghoshouni H, Ghaffary EM, Farzan M, Shaygannejad V, et al. Neurological efficacy and safety of mesenchymal stem cells (MSCs) therapy in people with multiple sclerosis (pwMS): An updated systematic review and meta-analysis. Mult Scler Relat Disord. 2024;87:105681. doi: 10.1016/j.msard.2024.105681.
21. Boffa G, Inglese M, Mancardi GL. Hematopoietic stem cell transplantation for multiple sclerosis. Handb Clin Neurol. 2024;202:153-167. doi: 10.1016/B978-0-323-90242-7.00011-0.
22. Nawar AA, Farid AM, Wally R, Tharwat EK, Sameh A, Elkaramany Y, et al. Efficacy and safety of stem cell transplantation for multiple sclerosis: a systematic review and meta-analysis of randomized controlled trials. Sci Rep. 2024;14(1):12545. doi:

10.1038/s41598-024-62726-4.
23. Jamali F, Aldughmi M, Atiani S, Al-Radaideh A, Dahbour S, Alhattab D, et al. Human Umbilical Cord-Derived Mesenchymal Stem Cells in the Treatment of Multiple Sclerosis Patients: Phase I/II Dose-Finding Clinical Study. Cell Transplant. 2024;33:9636897241233045. doi: 10.1177/09636897241233045.
24. Harris VK, Stark J, Williams A, Roche M, Malin M, Kumar A, et al. Efficacy of intrathecal mesenchymal stem cell-neural progenitor therapy in progressive MS: results from a phase II, randomized, placebo-controlled clinical trial. Stem Cell Res Ther. 2024;15(1):151. doi: 10.1186/s13287-024-03765-6. PMID: 38783390.
25. Pavlovic I, Zjukovskaja C, Nazir FH, Müller M, Wiberg A, Burman J. Cerebrospinal fluid mtDNA concentrations are increased in multiple sclerosis and were normalized after intervention with autologous hematopoietic stem cell transplantation. Mult Scler Relat Disord. 2024;84:105482. doi: 10.1016/j.msard.2024.105482.
26. Pastelín-Martínez ML, Gallardo-Pérez MM, Gómez-de-León A, Olivares-Gazca JC, Hernández-Flores EJ, Sánchez-Bonilla D, et al. The consequences of delayed diagnosis and treatment in persons with multiple sclerosis given autologous hematopoietic stem cell transplantation. Diagnosis (Berl). 2024. doi: 10.1515/dx-2023-0157.
27. Katsarogiannis E, Axelson H, Berntsson S, Rothkegel H, Burman J. Evoked potentials after autologous hematopoietic stem cell transplantation for multiple sclerosis. Mult Scler Relat Disord. 2024;83:105447. doi: 10.1016/j.msard.2024.105447.
28. Fan L, Zhang Y, Huang S, Chen J, Wang J, Meng F, et al. Effects of multiple treatments with stem cell therapy in patients with multiple sclerosis. Mult Scler Relat Disord. 2024;92:105944. doi: 10.1016/j.msard.2024.105944.
29. Noui Y, Zjukovskaja C, Silfverberg T, Ljungman P, Kultima K, Tolf A, et al. Factors associated with outcomes following autologous haematopoietic stem cell transplantation for multiple sclerosis. J Neurol Neurosurg Psychiatry. 2025:jnnp-2024-335512. doi: 10.1136/jnnp-2024-335512.
30. Hughes SL, Prettyjohns MJ, Snowden JA, Sharrack B. Economics of hematopoietic stem cell transplant in immune-mediated neurologic autoimmune diseases. Handb Clin Neurol. 2024;202:279-294. doi: 10.1016/B978-0-323-90242-7.00007-9.
31. Mariottini A, Nozzoli C, Carli I, Landi F, Gigli V, Repice AM, et al. Cost and effectiveness of autologous haematopoietic stem cell transplantation and high-efficacy disease-modifying therapies in relapsing-remitting multiple sclerosis. Neurol Sci. 2024. doi: 10.1007/s10072-024-07308-y.
32. Francesca S, De Marchi F, Mazzini L, Bendotti C. CELL THERAPY IN ALS: an update on preclinical and clinical studies. Brain Res Bull. 2023:S0361-9230(23)00012-6. doi: 10.1016/j.brainresbull.2023.01.008.
33. Nam JY, Chun S, Lee TY, Seo Y, Kim K, Park J, et al. Long-term survival benefits of intrathecal autologous bone marrow-derived mesenchymal stem cells (Neuronata-R®: lenzumestrocel) treatment in ALS: Propensity-score-matched control, surveillance study. Front Aging Neurosci. 2023;15:1148444. doi: 10.3389/fnagi.2023.1148444.
34. De Marchi F, Mareschi K, Ferrero I, Cantello R, Fagioli F, Mazzini L. Effect of mesenchymal stromal cell transplantation on long-term survival in amyotrophic lateral sclerosis. Cytotherapy. 2023:S1465-3249(23)00056-7. doi: 10.1016/j.jcyt.2023.02.005.
35. Crose JJ, Crose A, Ransom JT, Lightner AL. Bone marrow mesenchymal stem cell-derived extracellular vesicle infusion for amyotrophic lateral sclerosis. Neurodegener Dis Manag. 2024;14(3-4):111-117. doi: 10.1080/17582024.2024.2344396.
36. Al-Khayri JM, Ravindran M, Banadka A, Vandana CD, Priya K, Nagella P, Kukkemane K. Amyotrophic Lateral Sclerosis: Insights and New Prospects in Disease Pathophysiology, Biomarkers and Therapies. Pharmaceuticals (Basel). 2024;17(10):1391. doi: 10.3390/ph17101391.
37. Frawley L, Taylor NT, Sivills O, McPhillamy E, To TD, Wu Y, et al. Stem Cell Therapy for the Treatment of Amyotrophic Lateral Sclerosis: Comparison of the Efficacy of Mesenchymal Stem Cells, Neural Stem Cells, and Induced Pluripotent Stem Cells. Biomedicines. 2024;13(1):35. doi: 10.3390/biomedicines13010035.
38. Zhang J, Guo R, Zhou Z, Fu Z, Akogo HY, Li Y, et al. Neural Stem/Progenitor Cell Therapy in Patients and Animals with Amyotrophic Lateral Sclerosis: A Systematic Review and Meta-analysis. Mol Neurobiol. 2025. doi: 10.1007/s12035-024-04682-8.
39. Alkhazaali-Ali Z, Sahab-Negah S, Boroumand AR, Farkhad NK, Khodadoust MA, Ganjali R, Tavakol-Afshari J. Evaluation of Safety and Efficacy of Repeated Mesenchymal Stem Cell Transplantation in Patients with Amyotrophic Lateral Sclerosis (ALS) by Investigating Patient's Specific microRNAs as Novel Biomarkers: A Clinical Trial Study. Curr Stem Cell Res Ther. 2025. doi: 10.2174/011574888X330199250106081717.
40. Rangwala HS, Fatima H, Syed AM, Abbas SR, Rangwala BS. From Diagnosis to Treatment: A Comprehensive Review of Biomarkers and Therapeutic Advances in Parkinson's Disease. Ann Neurosci. 2025;32(1):51-57. doi: 10.1177/09727531231200733.
41. Marzookian K, Aliakbari F, Hourfar H, Sabouni F, Otzen DE, Morshedi D. The neuroprotective effect of human umbilical cord MSCs-derived secretome against α-synuclein aggregates on the blood-brain barrier. Int J Biol Macromol. 2025:140387. doi: 10.1016/j.ijbiomac.2025.140387.
42. Zhuo Y, Li X, He Z, Lu M. Pathological mechanisms of neuroimmune response and multitarget disease-modifying therapies of mesenchymal stem cells in Parkinson's disease. Stem Cell Res Ther. 2023;14(1):80. doi: 10.1186/s13287-023-03280-0.
43. Sun J, Zhang W, Wei ZZ, Song X, Jian L, Jiang F, et al. Mesenchymal stromal cell biotherapy for Parkinson's disease premotor symptoms. Chin Neurosurg J. 2023;9(1):28. doi: 10.1186/s41016-023-00338-z.
44. Jiang S, Wang H, Yang C, Feng F, Xu D, Zhang M,. Phase 1 study of safety and preliminary efficacy of intranasal transplantation of human neural stem cells (ANGE-S003) in Parkinson's disease. J Neurol Neurosurg Psychiatry. 2024:jnnp-2023-332921. doi: 10.1136/jnnp-2023-332921.
45. Tambe P, Undale V, Sanap A, Bhonde R, Mante N. The prospective role of mesenchymal stem cells in Parkinson's disease. Parkinsonism Relat Disord. 2024:107087. doi: 10.1016/j.parkreldis.2024.107087.
46. Zhao J, Qu K, Jia S, Yang R, Cui Z, Li J, et al. Efficacy and efficacy-influencing factors of stem cell transplantation on patients with Parkinson's disease: a systematic review and meta-analysis. Front Neurol. 2024;15:1329343. doi: 10.3389/fneur.2024.1329343.
47. Kim MS, Yoon S, Choi J, Kim YJ, Lee G. Stem Cell-Based Approaches in Parkinson's Disease Research. Int J Stem Cells. 2024. doi: 10.15283/ijsc23169.
48. Cattaneo E, Besusso D. Stem Cell Revolutions: An Alliance For Parkinson's Disease Driven By European Commission Consortia. Pharmacol Res. 2024:107569. doi: 10.1016/j.phrs.2024.107569.
49. Vij R, Kim H, Park H, Cheng T, Lotfi D, Chang D. Safety and efficacy of adipose-derived mesenchymal stem cell therapy in elderly Parkinson's disease patients: an intermediate-size expanded access program. Cytotherapy. 2024:S1465-3249(24)00885-5. doi: 10.1016/j.jcyt.2024.09.004.
50. Zhang S, Jiang X, Yan M, Cheng Z, Bi J, Wang Q, et al. Revealing induced pluripotent stem cells' potential as a better alternative to embryonic stem cells for Parkinson's disease treatment based on single-cell RNA-seq. Braz J Med Biol Res. 2024;57:e13482. doi: 10.1590/1414-431X2024e13482.
51. Yi LX, Woon HR, Saw G, Zeng L, Tan EK, Zhou ZD. Induced pluripotent stem cell-related approaches to generate dopaminergic neurons for Parkinson's disease. Neural Regen Res. 2024. doi: 10.4103/NRR.NRR-D-24-00771.
52. Khan MI, Jeong ES, Khan MZ, Shin JH, Kim JD. Stem cells-derived exosomes alleviate neurodegeneration and Alzheimer's pathogenesis by ameliorating neuroinflamation, and regulating the associated molecular pathways. Sci Rep. 2023;13(1):15731. doi: 10.1038/s41598-023-42485-4.
53. Gonçalves RGJ, Vasques JF, da Silva-Junior AJ, Gubert F, Mendez-Otero R. Mesenchymal stem cell- and extracellular vesicle-based therapies for Alzheimer's disease: progress, advantages, and challenges. Neural Regen Res. 2023;18(8):1645-1651. doi: 10.4103/1673-5374.361546.
54. Izayat EM, Shahien SA, El-Sherif AA, Hosney M. miRNAs and Stem Cells as Promising Diagnostic and Therapeutic Targets for Alzheimer's Disease. J Alzheimers Dis. 2023. doi: 10.3233/JAD-221298.
55. Pandey K, Khare P, Pandey SK, Johari S, Bhatnagar P, Sonane M, Mishra A. Stem Cells as a Novel Source for Regenerative Medicinal Applications in Alzheimer's Disease: An Update. Curr Mol Med. 2024. doi: 10.2174/0115665240334785240913071442.
56. Ou CM, Xue WW, Liu D, Ma L, Xie HT, Ning K. Stem cell therapy in Alzheimer's disease: current status and perspectives. Front Neurosci. 2024;18:1440334. doi: 10.3389/fnins.2024.1440334.
57. Șovrea AS, Boșca AB, Dronca E, Constantin AM, Crintea A, Suflețel R, Ștefan RA, Ștefan PA, Onofrei MM, Tschall C, Crivii CB. Non-Drug and Non-Invasive Therapeutic Options in Alzheimer's Disease. Biomedicines. 2025;13(1):84. doi: 10.3390/biomedicines13010084.
58. Peng D, Liu T, Lu H, Zhang L, Chen H, Huang Y, et al. Intranasal delivery of engineered extracellular vesicles loaded with miR-206-3p antagomir ameliorates Alzheimer's disease phenotypes. Theranostics. 2024;14(19):7623-7644. doi: 10.7150/thno.103596.
59. Pan Y, Li L, Cao N, Liao J, Chen H, Zhang M. Advanced nano delivery system for stem cell therapy for Alzheimer's disease. Biomaterials. 2024;314:122852. doi: 10.1016/j.biomaterials.2024.122852.
60. Abdi SMY, Al-Bakri SSM, Nordin N. Insights on the Characteristics and Therapeutic Potential of Mesenchymal Stem Cell-derived Exosomes for Mitigation of Alzheimer's Disease's Pathogenicity: A Systematic Review. Cell Biochem Biophys. 2024. doi: 10.1007/s12013-024-01598-x.
61. Jeyaraman M, Rajendran RL, Muthu S, Jeyaraman N, Sharma S, Jha SK, et al. An update on stem cell and stem cell-derived extracellular vesicle-based therapy in the management of Alzheimer's disease. Heliyon. 2023;9(7):e17808. doi: 10.1016/j.heliyon.2023.e17808.
62. Khan T, Waseem R, Shahid M, Ansari J, Ahanger IA, Hassan I, Islam A. Recent Advancement in Therapeutic Strategies for Alzheimer's Disease: Insights from Clinical Trials. Ageing Res Rev. 2023:102113. doi: 10.1016/j.arr.2023.102113.
63. Choi Y, Shin S, Son HJ, Lee NH, Myeong SH, Lee C, et al. Identification of potential biomarkers related to mesenchymal stem cell response in patients with Alzheimer's disease. Stem Cell Res Ther. 2023;14(1):178. doi: 10.1186/s13287-023-03410-8.
64. Oyebode OD, Tulay P. Mesenchymal Stem Cells Applications in Alzheimer's Disease. Glob Med Genet. 2023;10(4):382-387. doi: 10.1055/s-0043-1777087.
65. Feizi H, Hosseini MS, Seyedi-Sahebari S, Karimi H, Mosaddeghi-Heris R, Sadigh-Eteghad S, et al A systematic review of clinical efficacy and safety of cell-based therapies in Alzheimer's disease. Dement Neuropsychol. 2024;18:e20240147. doi: 10.1590/1980-5764-DN-2024-0147.
66. Bhatt A, Bhardwaj H, Shrivastava P. Mesenchymal stem cell therapy for Alzheimer's disease: A novel therapeutic approach for neurodegenerative diseases. Neuroscience. 2024:S0306-4522(24)00332-4. doi: 10.1016/j.neuroscience.2024.07.019.
67. Cao Z, Kong F, Ding J, Chen C, He F, Deng W. Promoting Alzheimer's disease research and therapy with stem cell technology. Stem Cell Res Ther. 2024;15(1):136. doi: 10.1186/s13287-024-03737-w.
68. Rash BG, Ramdas KN, Agafonova N, Naioti E, McClain-Moss L, Zainul Z, et al. Allogeneic mesenchymal stem cell therapy with laromestrocel in mild Alzheimer's disease: a randomized controlled phase 2a trial. Nat Med. 2025. doi: 10.1038/s41591-025-03559-0.
69. Bershteyn M, Bröer S, Parekh M, Maury Y, Havlicek S, Kriks S, et al. Human pallial MGE-type GABAergic interneuron cell therapy for chronic focal epilepsy. Cell Stem Cell 2023, 30: 1331-1350. e11.
70. Alayli A, Lockard G, Gordon J, Connolly J, Monsour M, Schimmel S, et al. Stem Cells: Recent Developments Redefining Epilepsy Therapy. Cell Transplant. 2023;32:9636897231158967. doi: 10.1177/09636897231158967.
71. Terman SW, Kirkpatrick L, Akiyama LF, Baajour W, Atilgan D, Dorotan MKC, et al. Current state of the epilepsy drug and device pipeline. Epilepsia. 2024. doi: 10.1111/epi.17884.
72. Zhou Y, Wang Y, Yang L. Stem Cell Transplantation Represents a New Strategy for the Treatment of Epilepsy. Neurosci Bull. 2024. doi: 10.1007/s12264-024-01208-z.

PERINATAL NEUROLOGICAL DISORDERS

HYPOXIC-ISCHEMIC ENCEPHALOPATHY (HIE)

It is a neurological complication of preterm birth, associated with high mortality and long-term complications, resulting in substantial personal, familial, medical, and socioeconomic burdens. The damage results from conditions that disrupt blood circulation and oxygenation of nervous tissue, leading to energy depletion and cell death in the affected area. When HIE is not fatal, the majority of patients develop neurological deficits, including hearing and vision loss, developmental delay, cerebral palsy, and epilepsy. Hypothermia is the primary current therapy, which must be initiated within the first hours after birth. While not without risks, its role is neuroprotective rather than neurorestorative (1). This devastating scenario underscores the urgent need for developing new strategies to manage HIE.

It is widely recognized that stem cells within the central nervous system can detect the microenvironment at the site of injury and secrete paracrine factors that promote repair. These factors regulate processes such as inflammation, oxidative stress, cell death, and fibrosis. For instance, various microRNAs (miRNAs) from stem cells and their derived exosomes modulate neuroinflammation, prevent cell death, promote neuronal repair, and enhance myelination. The most notable clinical outcomes include neuropsychological and motor improvement, a reduction in the severity and frequency of seizures, and a decreased need for anti-epileptic medications. Additionally, the combination of stem cell therapy with hypothermia appears to enhance therapeutic outcomes (2-9).

CEREBRAL PALSY AND GLOBAL DEVELOPMENT DELAY

Due to their neuroprotective and neuroregenerative potential, stem cell/exosome transplantation has emerged as an effective therapeutic alternative for improving various aspects of brain injury in children, including intellectual disability, global developmental delay, and cerebral palsy, when combined with conventional rehabilitation programs. Different clinical studies, including case series, controlled

clinical trials, and meta-analyses, conducted on hundreds of patients aged 6 months to 15 years have confirmed the safety and efficacy of various types of stem cells. Although there is still no consensus protocol regarding the optimal cell source, dosage, route of administration, timing, and frequency of applications, most studies have reported positive responses in cognitive function, language, self-care, motor function, neck control, seated balance, postural tone, seizure frequency, social adaptability, and quality of life. Subgroup analyses indicate that umbilical cord-derived cells and intrathecal administration yield better outcomes. Additionally, younger children and those with less severe disabilities tend to respond more favorably. Adverse events have been minimal and temporary (10-18).

REFERENCES

1. Sato Y, Shimizu S, Ueda K, Suzuki T, Suzuki S, Miura R, et al. Safety and tolerability of a Muse cell-based product in neonatal hypoxic-ischemic encephalopathy with therapeutic hypothermia (SHIELD trial). Stem Cells Transl Med. 2024:szae071. doi: 10.1093/stcltm/szae071.

2. Thébaud B. Stem cell therapies for neonatal lung diseases: Are we there yet? Semin Perinatol. 2023:151724. doi: 10.1016/j.semperi.2023.151724.

3. Abe Y, Sato Y, Tanaka M, Ochiai D. Development of a new treatment for preterm birth complications using amniotic fluid stem cell therapy. Histol Histopathol. 2023:18607. doi: 10.14670/HH-18-607.

4. Luo BY, Zhou HS, Sun YF, Xiao QX, Chen L, She HQ, et al. The fate and prospects of stem cell therapy in the treatment of hypoxic-ischemic encephalopathy. Eur J Neurosci. 2023. doi: 10.1111/ejn.16040.

5. Cotten CM, Fisher K, Malcolm W, Gustafson KE, Cheatham L, Marion A, et al. A Pilot Phase I Trial of Allogeneic Umbilical Cord Tissue-Derived Mesenchymal Stromal Cells in Neonates With Hypoxic-Ischemic Encephalopathy. Stem Cells Transl Med. 2023:szad027. doi: 10.1093/stcltm/szad027.

6. Mintoft A, Vallatos A, Robertson NJ. Mesenchymal Stromal Cell therapy for Hypoxic Ischemic Encephalopathy: Future directions for combination therapy with hypothermia and/or melatonin. Semin Perinatol. 2024:151929. doi: 10.1016/j.semperi.2024.151929.

7. Al-Ward H, Chen W, Gao W, Zhang C, Yang X, Xiong Y, et al. Can miRNAs in MSCs-EVs Offer a Potential Treatment for Hypoxic-ischemic Encephalopathy? Stem Cell Rev Rep. 2024. doi: 10.1007/s12015-024-10803-6.

8. Milczarek O, Jarocha D, Starowicz-Filip A, Kasprzycki M, Kijowski J, Mordel A, et al. Bone Marrow Nucleated Cells and Bone Marrow-Derived CD271+ Mesenchymal Stem Cell in Treatment of Encephalopathy and Drug-Resistant Epilepsy. Stem Cell Rev Rep. 2024. doi: 10.1007/s12015-023-10673-4.

9. Yang M, Wang K, Liu B, Shen Y, Liu G. Hypoxic-Ischemic Encephalopathy: Pathogenesis and Promising Therapies. Mol Neurobiol. 2024. doi: 10.1007/s12035-024-04398-9.

10. Qu J, Zhou L, Zhang H, Han D, Luo Y, Chen J, et al. Efficacy and safety of stem cell therapy in cerebral palsy: A systematic review and meta-analysis. Front Bioeng Biotechnol. 2022;10:1006845. doi: 10.3389/fbioe.2022.1006845.

11. Zarrabi M, Akbari MG, Amanat M, Majmaa A, Moaiedi AR, Montazerlotfelahi H, et al. The safety and efficacy of umbilical cord blood mononuclear cells in individuals with spastic cerebral palsy: a randomized double-blind sham-controlled clinical trial. BMC Neurol. 2022;22(1):123. doi: 10.1186/s12883-022-02636-y.

12. Suh MR, Min K, Cho KH, Kim J, Lim I, Park M, et al. Maintenance of the synergistic effects of cord blood cells and erythropoietin combination therapy after additional cord blood infusion in children with cerebral palsy: 1-year open-label extension study of randomized placebo-controlled trial. Stem Cell Res Ther. 2023;14(1):362. doi: 10.1186/s13287-023-03600-4.

13. Lv Z, Li Y, Wang Y, Cong F, Li X, Cui W, et al. Safety and efficacy outcomes after intranasal administration of neural stem cells in cerebral palsy: a randomized phase 1/2 controlled trial. Stem Cell Res Ther. 2023;14(1):23. doi: 10.1186/s13287-022-03234-y.

14. Yousif NG, Yousif MG, Mohsen AAU, El-Bakaa HS, Younise MH, Altimimi AN, et al. Prospective single center analysis of outcome stem cells transplants in patients with cerebral palsy. Pol Merkur Lekarski. 2023;51(4):339-345. doi: 10.36740/Merkur202304107.

15. Chrościńska-Kawczyk M, Zdolińska-Malinowska I, Boruczkowski D. The Impact of Umbilical Cord Mesenchymal Stem Cells on Motor Function in Children with Cerebral Palsy: Results of a Real-world, Compassionate use Study. Stem Cell Rev Rep. 2024. doi: 10.1007/s12015-024-10742-2.

16. Finch-Edmondson M, Paton MCB, Webb A, Reza Ashrafi M, Blatch-Williams RK, Cox CS Jr, et al. Cord Blood Treatment for Children With Cerebral Palsy: Individual Participant Data Meta-Analysis. Pediatrics. 2025:e2024068999. doi: 10.1542/peds.2024-068999.

17. Li X, Li M, Qin X, Li Y, Wang Y, Han C, et al. Providing holistic care to children with cerebral palsy treated with transnasal neural stem cell transplantation. Front Pediatr. 2024;11:1297563. doi: 10.3389/fped.2023.1297563.

18. Nouri M, Zarrabi M, Masoumi S, Khodadoust E, Majmae A, Amanat M, et al. Cell-Based Therapy for Cerebral Palsy: A Puzzle in Progress. Cell J. 2025;26(9):569-574. doi: 10.22074/cellj.2024.2032098.1600.

AUTISM SPECTRUM DISORDERS (AUTISM)

Autism spectrum disorders (ASD) are a group of clinical conditions characterized by impairments in communication, cognition, perception, motor skills, executive function, and emotional regulation. Although the pathophysiology remains unclear, evidence suggests immune system dysfunction and neuroinflammation originating in prenatal life. This process, known as “maternal immune activation” is triggered by inflammation during pregnancy and induces inflammatory signals that disrupt neurodevelopment and cause structural abnormalities in the fetal brain. Elevated levels of inflammatory markers from pro-inflammatory cells have been found in the blood of individuals with autism compared to normal controls (1-3).

Current treatment options are scarce and primarily focused on symptom management, highlighting the need to explore new therapeutic strategies. Based on growing evidence that autism is a neuroimmune disorder, new possibilities arise for treatment with agents that modulate neuroinflammation. In this context, the anti-inflammatory and immunomodulatory properties of stem cells/exosomes emerge as a promising therapeutic option for enhancing brain function in patients with autism (4,5). An increasing number of individual studies and meta-analyses have investigated the effects of these cells in patients with ASD, reporting benefits in biochemical markers of neuroinflammation and in severity scales of ASD symptoms (including language, social communication, repetitive behavior, and hyperactivity) in patients aged 2 to 15 years. Notably, no serious adverse effects related to the intervention have been reported in any of the clinical studies published to date (6-10).

REFERENCES

1. Nabetani M, Mukai T, Taguchi A. Cell Therapies for Autism Spectrum Disorder Based on New Pathophysiology: A Review. Cell Transplant. 2023;32:9636897231163217. doi: 10.1177/09636897231163217.

2. Takada R, Toritsuka M, Yamauchi T, Ishida R, Kayashima Y, Nishi Y, et al. Granulocyte macrophage colony-stimulating factor-induced macrophages of individuals with autism spectrum disorder adversely affect neuronal dendrites through the secretion of pro-inflammatory cytokines. Mol Autism. 2024;15(1):10. doi: 10.1186/s13229-024-00589-2.

3. Vacharasin JM, Ward JA, McCord MM, Cox K, Imitola J, Lizarraga SB. Neuroimmune mechanisms in autism etiology - untangling a complex problem using human cellular models. Oxf Open Neurosci. 2024;3:kvae003. doi: 10.1093/oons/kvae003.

4. Darwish M, El Hajj R, Khayat L, Alaaeddine N. Stem Cell Secretions as a Potential Therapeutic Agent for Autism Spectrum Disorder: A Narrative Review. Stem Cell Rev Rep. 2024. doi: 10.1007/s12015-024-10724-4.

5. Wikarska A, Roszak K, Roszek K. Mesenchymal Stem Cells and Purinergic Signaling in Autism Spectrum Disorder: Bridging the Gap between Cell-Based Strategies and Neuro-Immune Modulation. Biomedicines. 2024;12(6):1310. doi: 10.3390/biomedicines12061310.

6. Qu J, Liu Z, Li L, Zou Z, He Z, Zhou L, et al. Efficacy and Safety of Stem Cell Therapy in Children With Autism Spectrum Disorders: A Systematic Review and Meta-Analysis. Front Pediatr. 2022;10:897398. doi: 10.3389/fped.2022.897398.

7. Shamim S, Khan N, Greene DL, Habiba UE, Umer A. The promise of autologous and allogeneic cellular therapies in the clinical trials of autism spectrum disorder. Regen Med. 2023. doi: 10.2217/rme-2022-0176.

8. Cha B, Kwak H, Bang JI, Jang SJ, Suh MR, Choi JI, et al. Safety and efficacy of allogeneic umbilical cord blood therapy for global development delay and intellectual disability. Stem Cells Dev. 2023. doi: 10.1089/scd.2022.0252.

9. Kale G, Addepalli V, Joshi S. A snapshot on introspection of autism spectrum disorder. Mol Biol Rep. 2024;51(1):610. doi: 10.1007/s11033-024-09514-5.

10. Kabatas S, Civelek E, Savrunlu EC, Karaaslan U, Yıldız Ö, Karaöz E. Advances in the treatment of autism spectrum disorder: Wharton jelly mesenchymal stem cell transplantation. World J Methodol. 2025;15(1):95857. doi: 10.5662/wjm.v15.i1.95857.

STROKE

Currently, there is no effective treatment for conditions involving the death of neurons and glial cells, as the regenerative capacity of nervous tissue is very limited. Consequently, a major focus of the scientific and clinical communities is on minimizing damage, promoting the reconstruction of nervous tissue, and restoring its structure and function following injury (1). Stroke is the most common neurological disorder in adults, and its incidence has risen primarily due to population aging and the growing prevalence of cardiovascular disease. In addition, current interventions to manage acute stroke have helped reduce mortality. However, many patients are left with residual cognitive, sensory, and/or motor impairments. Therefore, interventions aimed at preventing stroke, treating its acute phase, or addressing its sequelae are being actively explored. Stem cell/exosome based regenerative therapy represents a novel approach to reducing stroke-related disability.

Although the therapeutic mechanism of action of stem cells/exosomes in ***ischemic stroke*** is not yet fully understood, it is known to involve: a) the release of factors that increase neuronal survival (neurotrophic) and the formation of new blood vessels (angiogenic); b) inhibition of inflammation and the immune response triggered by ischemia; c) regeneration of myelin (the insulating layer surrounding neurons, essential for efficient inter-neuronal communication); d) restoration of the blood-brain barrier (which prevents potentially harmful substances from entering the brain), whose disruption following stroke further impairs neurological function; stem cells/exosomes have been shown to help restore the integrity of this barrier during the acute phase of stroke (2-6).

The safety and functional improvement of stem cell/exosome therapy has already been confirmed in animal models of ischemic stroke (7). Evidence in humans has been accumulating rapidly, to the point that the risk-benefit profile of regenerative medicine approaches for the treatment of various forms of ischemic stroke leaves little doubt. Stem cell transplantation in acute, subacute, and chronic ischemic stroke is considered safe and has been associated with neurological improvement, as measured by significant clinical outcomes including severe disability, recurrent stroke, and

mortality. This therapeutic potential also extends to cerebral small vessel disease, a condition with unclear pathogenesis that is linked to cognitive impairment and dementia. A favorable safety and efficacy profile has been reported for stem cell therapy administered through various routes and at different doses during the acute, subacute, and chronic phases of ischemic stroke. Regarding the routes of administration, intravenous therapy appears to be the safest option during the acute and subacute phases, while the intrathecal route is preferred in the chronic phase. Intracarotid infusion has also been utilized in the acute phase (8,9). The current evidence includes randomized controlled trials, systematic reviews, and large meta-analyses (10–18).

REFERENCES

1. Pappolla MA, Wu P, Fang X, Poeggeler B, Sambamurti K, Wisniewski T, Perry G. Stem Cell Interventions in Neurology: From Bench to Bedside. J Alzheimers Dis. 2024;101(s1):S395-S416. doi: 10.3233/JAD-230897.

2. Zhu P, Tan H, Gao H, Wang J, Liu Y, Yang D, Wu T. Potential Mechanism and Perspectives of Mesenchymal Stem Cell Therapy for Ischemic Stroke: A Review. Glob Med Genet. 2024;11(4):278-284. doi: 10.1055/s-0044-1790231.

3. Vagionitis S, Káradóttir RT. Functional implication for myelin regeneration in recovery from ischaemic stroke. Brain. 2024;147(4):1118-1120. doi: 10.1093/brain/awae080.

4. Song J, Zhou D, Cui L, Wu C, Jia L, Wang M, et al. Advancing stroke therapy: innovative approaches with stem cell-derived extracellular vesicles. Cell Commun Signal. 2024;22(1):369. doi: 10.1186/s12964-024-01752-1.

5. Li Y, Chen J, Quan X, Chen Y, Han Y, Chen J, et al. Extracellular Vesicles Maintain Blood-Brain Barrier Integrity by the Suppression of Caveolin-1/CD147/VEGFR2/MMP Pathway After Ischemic Stroke. Int J Nanomedicine. 2024;19:1451-1467. doi: 10.2147/IJN.S444009.

6. Sprincl V, Romanyuk N. miRNA in blood-brain barrier repair: role of extracellular vesicles in stroke recovery. Front Cell Neurosci. 2025;19:1503193. doi: 10.3389/fncel.2025.1503193.

7. Zhang X, Guo Y, Fang K, Huang X, Lan D, Wang M, et al. Therapeutic Potential of Mesenchymal Stem Cell-Derived Extracellular Vesicles in Ischemic Stroke: A Meta-Analysis of Preclinical Studies. Brain Res Bull. 2025:111219. doi: 10.1016/j.brainresbull.2025.111219.

8. Habib P, Steinberg GK. Clinical state and future directions of stem cell therapy in stroke rehabilitation. Exp Neurol. 2024:115132. doi: 10.1016/j.expneurol.2024.115132.

9. Ya J, Pellumbaj J, Hashmat A, Bayraktutan U. The Role of Stem Cells as Therapeutics for Ischaemic Stroke. Cells. 2024;13(2):112. doi: 10.3390/cells13020112.

10. Waseem A, Saudamini, Haque R, Janowski M, Raza SS. Mesenchymal stem cell-derived exosomes: Shaping the next era of stroke treatment. Neuroprotection. 2023:99-116. doi: 10.1002/nep3.30.

11. Lin HS, Sung PH, Huang SH, Lin WC, Chiang JY, Ma MC, et al. Long term outcomes of intracarotid arterial transfusion of circulatory-derived autologous CD34 + cells for acute ischemic stroke patients-A randomized, open-label, controlled phase II clinical trial. Stem Cell Res Ther. 2024;15(1):443. doi: 10.1186/s13287-024-04021-7.

12. Shen Z, Tang X, Zhang Y, Jia Y, Guo X, Guo X, et al. Efficacy and safety of mesenchymal stem cell therapies for ischemic stroke: a systematic review and meta-analysis. Stem Cells Transl Med. 2024:szae040. doi: 10.1093/stcltm/szae040.

13. Xiong Y, Guo X, Gao W, Ke C, Huang X, Pan Z, et al. Efficacy and safety of stem cells in the treatment of ischemic stroke: A meta-analysis. Medicine (Baltimore). 2024;103(12):e37414. doi: 10.1097/MD.0000000000037414. PMID: 38518043.

14. Chen DH, Huang JR, Su SL, Chen Q, Wu BY. Therapeutic potential of mesenchymal stem cells for cerebral small vessel disease. Regen Ther. 2024;25:377-386. doi: 10.1016/j.reth.2023.11.002.

15. Afshar Hezarkhani L, Veysi K, Rahmani A, Salari N, Hasheminezhad R, Nasr V, Mohammadi M. Safety and Efficacy of Bone Marrow and Adipose Tissue-Derived Mesenchymal Stem Cells for the Treatment of Ischemic Stroke: A Systematic Review. Cardiol Rev. 2024. doi: 10.1097/CRD.0000000000000671.

16. Pratiwi DIN, Alhajlah S, Alawadi A, Hjazi A, Alawsi T, Almalki SG, et al. Mesenchymal stem cells and their extracellular vesicles as emerging therapeutic tools in the treatment of ischemic stroke. Tissue Cell. 2024;87:102320. doi: 10.1016/j.tice.2024.102320.

17. Mulia GJ, Anna N, Wu JC, Ma HP, Chiang YH, Ou JC, Chen KY. Stem Cell-Based Therapies via Different Administration Route for Stroke: A Meta-analysis of Comparative Studies. Cell Transplant. 2025;34:9636897251315121. doi: 10.1177/09636897251315121.

18. Alrasheed AS, Aljahdali TA, Alghafli IA, Alghafli GA, Almuslim MF, AlMohish NM, et al. Safety and Efficacy of Stem Cell Therapy in Ischemic Stroke: A Comprehensive Systematic Review and Meta-Analysis. J Clin Med. 2025;14(6):2118. doi: 10.3390/jcm14062118.

CENTRAL NERVOUS SYSTEM INJURIES

Due to the limited regenerative capacity of the central nervous system (CNS), one of the most prominent features of stem cell/exosome based regenerative medicine is its potential to replace lost neurons and reconstruct neuronal circuits. In addition, these therapies exert paracrine and immunomodulatory effects in a variety of neurological disorders, including CNS injuries (1,2).

TRAUMATIC BRAIN INJURY

It is the brain damage caused by an external force, leading to physical and cognitive dysfunction. Traditional therapeutic approaches have produced limited results, and only recently have stem cells/exosomes emerged as a promising treatment option (3).

The precise biological mechanism by which stem cells/exosomes reduce neurological deficits and cognitive sequelae following traumatic brain injury is not yet fully understood. However, studies in animal models of brain trauma have shown that early administration of exosomes (within 90 minutes post-injury) can prevent neuroinflammation, preserve neurogenesis, and avoid the loss of inter-neuronal connections. These effects are accompanied by an increase in the concentration of brain-derived neurotrophic factor (BDNF), the principal neurotrophic factor in the brain (4).

Clinical studies to date have shown that stem cell/exosome therapy, administered through intrathecal, intravenous, or intranasal routes, is more effective than conventional treatments: Patients exhibit improvements in cognitive function, muscle spasticity, muscle strength, and fine motor skills, along with radiological findings and biological markers (5,6).

SPINAL CORD INJURY

It can be a devastating condition, leading to sensory, motor, and autonomic dysfunction below the level of the injury. Immediately after the trauma, a cascade of events, known as “secondary injury” is triggered, involving hemorrhage, ischemia-reperfusion injury, oxidative stress, neuroinflammation, and degeneration of nervous tissue. Conventional treatment modalities have very limited effectiveness (7).

In spinal cord injury, stem cells and their exosomes promote angiogenesis and axonal growth, modulate inflammation and immune responses, exert analgesic effects, regulate cell death, and preserve the integrity of the blood–brain barrier (7–12). For these reasons, regenerative therapy has become a therapeutic option with increasing scientific support. Indeed, the literature confirms its safety and efficacy through a range of studies, from small clinical trials to large-scale

meta-analyses involving hundreds of patients. As a result, the use of stem cells in brain and spinal cord injuries has already been authorized by health regulatory agencies in several countries (13).

The reported benefits of stem cells/exosomes include functional improvement and enhanced quality of life during the acute, subacute, and chronic phases of spinal cord injury (14–19). Moreover, the safety of the procedure has been demonstrated across multiple routes of administration, at various spinal levels, and over a broad range of dosing regimens. In this regard, a particularly noteworthy statement from the authors of a recent review and meta-analysis on the topic reads: "We concluded that the frequency of life-threatening adverse events following cell therapy clinical trials in chronic spinal cord injury patients is very scarce and can be ignored" (20-23).

REFERENCES

1. Montoto-Meijide R, Meijide-Faílde R, Díaz-Prado SM, Montoto-Marqués A. Mesenchymal Stem Cell Therapy in Traumatic Spinal Cord Injury: A Systematic Review. Int J Mol Sci. 2023;24(14):11719. doi: 10.3390/ijms241411719.

2. Rahimi Darehbagh R, Seyedoshohadaei SA, Ramezani R, Rezaei N. Stem cell therapies for neurological disorders: current progress, challenges, and future perspectives. Eur J Med Res. 2024;29(1):386. doi: 10.1186/s40001-024-01987-1.

3. Saboori M, Riazi A, Taji M, Yadegarfar G. Traumatic brain injury and stem cell treatments: A review of recent 10 years clinical trials. Clin Neurol Neurosurg. 2024;239:108219. doi: 10.1016/j.clineuro.2024.108219.

4. Kodali M, Madhu LN, Reger RL, Milutinovic B, Upadhya R, Attaluri S, et al. A single intranasal dose of human mesenchymal stem cell-derived extracellular vesicles after traumatic brain injury eases neurogenesis decline, synapse loss, and BDNF-ERK-CREB signaling. Front Mol Neurosci. 2023;16:1185883. doi: 10.3389/fnmol.2023.1185883.

5. Kabatas S, Civelek E, Boyalı O, Sezen GB, Ozdemir O, Bahar-Ozdemir Y, et al. Safety and efficiency of Wharton's Jelly-derived mesenchymal stem cell administration in patients with traumatic brain injury: First results of a phase I study. World J Stem Cells. 2024;16(6):641-655. doi: 10.4252/wjsc.v16.i6.641.

6. Zhang Y, Zheng Z, Sun J, Xu S, Wei Y, Ding X, Ding G. The application of mesenchymal stem cells in the treatment of traumatic brain injury: mechanisms, results, and problems. Histol Histopathol. 2024:18716. doi: 10.14670/HH-18-716.

7. Huang LY, Sun X, Pan HX, Wang L, He CQ, Wei Q. Cell transplantation therapies for spinal cord injury focusing on bone marrow mesenchymal stem cells: Advances and challenges. World J Stem Cells. 2023;15(5):385-399. doi: 10.4252/wjsc.v15.i5.385.

8. Chen SY, Yang RL, Wu XC, Zhao DZ, Fu SP, Lin FQ, et al. Mesenchymal Stem Cell Transplantation: Neuroprotection and Nerve Regeneration After Spinal Cord Injury. J Inflamm Res. 2023;16:4763-4776. doi: 10.2147/JIR.S428425.

9. Zeng CW. Advancing Spinal Cord Injury Treatment through Stem Cell Therapy: A Comprehensive Review of Cell Types, Challenges, and Emerging Technologies in Regenerative Medicine. Int J Mol Sci. 2023;24(18):14349. doi: 10.3390/ijms241814349.

10. An J, Chen B, Zhang R, Tian D, Shi K, Zhang L, et al. Therapeutic Potential of Mesenchymal Stem Cell-Derived Exosomes in Spinal Cord Injury. Mol Neurobiol. 2024. doi: 10.1007/s12035-024-04490-0.

11. Yarahmadi A, Dorri Giv M, Hosseininejad R, Rezaie A, Mohammadi N, Afkhami H, et al. Mesenchymal stem cells and their extracellular vesicle therapy for neurological disorders: traumatic brain injury and beyond. Front Neurol. 2025;16:1472679. doi: 10.3389/fneur.2025.1472679.

12. Zeng CW. Stem Cell-Based Approaches for Spinal Cord Injury: The Promise of iPSCs. Biology (Basel). 2025;14(3):314. doi: 10.3390/biology14030314.

13. Liu R, Peng B, Yuan J, Hu J, Yang J, Shan N, et al. Research on stem cell therapy for spinal cord injury: a bibliometric and visual analysis from 2018-2023. Front Genet. 2024;15:1327216. doi: 10.3389/fgene.2024.1327216.

14. Xia Y, Zhu J, Yang R, Wang H, Li Y, Fu C. Mesenchymal stem cells in the treatment of spinal cord injury: Mechanisms, current advances and future challenges. Front Immunol. 2023;14:1141601. doi: 10.3389/fimmu.2023.1141601.

15. Hirota R, Sasaki M, Iyama S, Kurihara K, Fukushi R, Obara H, et al. Intravenous Infusion of Autologous Mesenchymal Stem Cells Expanded in Auto Serum for Chronic Spinal Cord Injury Patients: A Case Series. J Clin Med. 2024;13(20):6072. doi: 10.3390/jcm13206072.

16. Akhlaghpasand M, Tavanaei R, Hosseinpoor M, Yazdani KO, Soleimani A, Zoshk MY, et al. Safety and potential effects of intrathecal injection of allogeneic human umbilical cord mesenchymal stem cell-derived exosomes in complete subacute spinal cord injury: a first-in-human, single-arm, open-label, phase I clinical trial. Stem Cell Res Ther. 2024;15(1):264. doi: 10.1186/s13287-024-03868-0.

17. Zhang C. Exosomes Derived from Mesenchymal Stem Cells: Therapeutic Opportunities for Spinal Cord Injury. Bull Exp Biol Med. 2024. doi: 10.1007/s10517-024-06095-y.

18. Yu T, Yang LL, Zhou Y, Wu MF, Jiao JH. Exosome-mediated repair of spinal cord injury: a promising therapeutic strategy. Stem Cell Res Ther. 2024;15(1):6. doi: 10.1186/s13287-023-03614-y.

19. Sugai K, Nakamura M, Okano H, Nagoshi N. Stem cell therapies for spinal cord injury in humans: A review of recent clinical research. Brain Spine. 2025;5:104207. doi: 10.1016/j.bas.2025.104207.

20. Ralph PC, Choi SW, Back MJ, Lee SJ. Regenerative Medicine Approaches for the Treatment of Spinal Cord Injuries: Progress and Challenges. Acta Biomater. 2024:S1742-7061(24)00613-5. doi: 10.1016/j.actbio.2024.10.021.

21. Macêdo CT, de Freitas Souza BS, Villarreal CF, Silva DN, da Silva KN, de Souza CLEM, et al. Transplantation of autologous mesenchymal stromal cells in complete cervical spinal cord injury: a pilot study. Front Med (Lausanne). 2024;11:1451297. doi: 10.3389/fmed.2024.1451297.

22. Davoudi-Monfared E, Abolghasemi R, Allahyari F, Farzanegan G. Adverse events of cell therapy clinical trials in human chronic spinal cord injury, a systematic review and meta-analysis. Regen Ther. 2024;27:381-397. doi: 10.1016/j.reth.2024.03.012.

23. Bydon M, Qu W, Moinuddin FM, Hunt CL, Garlanger KL, Reeves RK, et al. Intrathecal delivery of adipose-derived mesenchymal stem cells in traumatic spinal cord injury: Phase I trial. Nat Commun. 2024;15(1):2201. doi: 10.1038/s41467-024-46259-y.

INFERTILITY

FEMALE INFERTILITY

Female infertility, defined as the inability to achieve pregnancy despite regular sexual intercourse for at least 12 months, has multiple underlying causes, and treatment options vary depending on the specific type of infertility. Premature ovarian failure (POF, defined as amenorrhea before the age of 40, accompanied by endocrine disturbances and menopausal symptoms), endometrial disorders (such as intrauterine adhesions and thin endometrium), and polycystic ovary syndrome (characterized by elevated masculine hormones, ovulation abnormalities, and insulin resistance) are among the most common causes of female infertility. Stem cell/exosome therapies have increasingly been established as innovative treatment options for these conditions (1–3).

Although the exact mechanism of action in POF remains unclear, *in vitro* and animal studies have demonstrated that various types of stem cells promote follicular growth, maturation, and viability of cultured follicles (4). In women, stem cells improve ovarian function, with greater benefits observed in patients with amenorrhea lasting less than one year. According to some authors, current evidence has demonstrated that cellular therapy is the most effective approach for treating POF compared to other therapeutic options, as it improves pregnancy rates and results in the birth of healthy babies (5–14).

Recurrent implantation failure is defined as the inability to achieve pregnancy after three or more embryo transfer attempts (15). Two common causes of this condition are a local predominance of pro-inflammatory factors due to immune system imbalance, and the accumulation of fibrotic tissue in the endometrium, leading to partial or complete obstruction of the uterine cavity (16,17). Additionally, biochemical and cellular studies have shown that endometrial stem cells from women with endometrial atrophy and intrauterine adhesions are prone to differentiate into pro-fibrotic cell types. In these cases, stem cell/exosome therapy helps regulate local inflammation, improves endometrial thickness and integrity, and increases implantation rates and the likelihood of pregnancy (2,15,18–22).

In women with polycystic ovary syndrome, intra-ovarian injection of stem cells has been associated with reduced androgen levels, restoration of insulin sensitivity, and decreased inflammatory markers (2,23,24).

ERECTILE DYSFUNCTION

Erectile dysfunction is caused by endothelial dysfunction and impaired neural conductivity, often associated with neuropathy and microangiopathy secondary to nervous system trauma, atherosclerosis, diabetes, and other age-related conditions. While the evidence supporting the benefits of regenerative medicine for this clinical condition remains limited, several reports have confirmed the effectiveness and rapid response to intracavernosal administration of stem cells/exosomes. Moreover, their therapeutic effect appears to be enhanced when combined with established treatments such as phosphodiesterase type 5 inhibitors (e.g., sildenafil) or low-intensity extracorporeal shock wave therapy (LI-ESWT). There is also some evidence that stem cells may promote nerve and vascular regeneration, beyond merely alleviating symptoms (25–32).

REFERENCIAS

1. Hu L, Tan R, He Y, Wang H, Pu D, Wu J. Stem cell therapy for premature ovarian insufficiency: a systematic review and meta-analysis of animal and clinical studies. Arch Gynecol Obstet. 2023. doi: 10.1007/s00404-023-07062-0.
2. Gao G, Li L, Li C, Liu D, Wang Y, Li C. Mesenchymal stem cells: Guardians of women's health. Regen Ther. 2024;26:1087-1098. doi: 10.1016/j.reth.2024.10.011.
3. Vakili S, Jafarinia M. Advances in Mesenchymal Stem Cell Research Applications for Female Infertility-Mechanisms, Efficacy Parameters, Challenges and Future Roadmap. Galen Med J. 2024;13:1-10. doi: 10.31661/gmj.v13i.3632.
4. Cui X, Jing X. Stem cell-based therapeutic potential in female ovarian aging and infertility. J Ovarian Res. 2024;17(1):171. doi: 10.1186/s13048-024-01492-3.
5. Hu L, Tan R, He Y, Wang H, Pu D, Wu J. Stem cell therapy for premature ovarian insufficiency: a systematic review and meta-analysis of animal and clinical studies. Arch Gynecol Obstet. 2023. doi: 10.1007/s00404-023-07062-0.
6. Buigues A, Ramírez-Martin N, Martínez J, Pellicer N, Meseguer M, Pellicer A, et al. Systemic changes induced by autologous stem cell ovarian transplant in plasma proteome of women with impaired ovarian reserves. Aging (Albany NY). 2023;15(24):14553-14573. doi: 10.18632/aging.205400.
7. Sadeghi S, Mosaffa N, Huang B, Ramezani Tehrani F. Protective role of stem cells in POI: Current status and mechanism of action, a review article. Heliyon. 2023;10(1):e23271. doi: 10.1016/j.heliyon.2023.e23271.
8. Kuchakzadeh F, Ai J, Ebrahimi-Barough S. Tissue engineering and stem cell-based therapeutic strategies for premature ovarian insufficiency. Regen Ther. 2023;25:10-23. doi: 10.1016/j.reth.2023.11.007.
9. Ljubić A, Dinić M, Švraka D, Vujović S. Dual-Double Stem Cell Ovarian Therapy: A Comprehensive Approach in Regenerative Medicine. Int J Mol Sci. 2024;26(1):69. doi: 10.3390/ijms26010069.
10. Yahyavi Y, Kheradi N, Karimi A, Ebrahimi-Kalan A, Ramezani F, Yousefi S, et al. Novel Advances in Cell-Free Therapy for Premature Ovarian Failure (POF): A Comprehensive Review. Adv Pharm Bull. 2024;14(3):543-557. doi: 10.34172/apb.2024.059.
11. Umer A, Ahmad K, Khan N, Greene DL, Shamim S, Habiba UE. Meta-analysis highlight the therapeutic potential of stem cells for premature ovarian failure. Regen Ther. 2024;26:478-488. doi: 10.1016/j.reth.2024.07.001
12. Saharkhiz N, Hajizadeh N, Alkhafaji JS, Mohammadi MH. Evaluation of the therapeutic effect of very small stem cells from peripheral blood on the treatment of Premature Ovarian Failure: A pilot study. JBRA Assist Reprod. 2024. doi: 10.5935/1518-0557.20240021.
13. Kim HK, Kim TJ. Current Status and Future Prospects of Stem Cell Therapy for Infertile Patients with Premature Ovarian Insufficiency. Biomolecules. 2024;14(2):242. doi: 10.3390/biom14020242.
14. Hu HQ, Xin XY, Zhu YT, Fan RW, Zhang HL, Ye Y, Li D. Application of mesenchymal stem cell therapy for premature ovarian insufficiency: Recent advances from mechanisms to therapeutics. World J Stem Cells. 2024;16(1):1-6. doi: 10.4252/wjsc.v16.i1.1.
15. Garmendia JV, De Sanctis CV, Hajdúch M, De Sanctis JB. Exploring the Immunological Aspects and Treatments of Recurrent Pregnancy Loss and Recurrent Implantation Failure. Int J Mol Sci. 2025;26(3):1295. doi: 10.3390/ijms26031295.
16. Song J, Li M, Tao Y, Li Y, Mai C, Zhang J, et al. Enhanced myofibroblast differentiation of eMSCs in intrauterine adhesions. Stem Cell Res Ther. 2025;16(1):35. doi: 10.1186/s13287-025-04183-y.
17. Zheng X, Huang R, Yin L, Yao M, Chu J, Yang F, et al. Injectable antioxidant hyaluronan/chitosan hydrogel as a platelet-rich plasma and stem cell carrier to promote endometrial regeneration and fertility restoration. Acta Biomater. 2025:S1742-7061(25)00082-0. doi: 10.1016/j.actbio.2025.01.062.
18. Hu L, Tan R, He Y, Wang H, Pu D, Wu J. Stem cell therapy for premature ovarian insufficiency: a systematic review and meta-analysis of animal and clinical studies. Arch Gynecol Obstet. 2023. doi: 10.1007/s00404-023-07062-0.
19. Mohamed Rasheed ZB, Nordin F, Wan Kamarul Zaman WS, Tan YF, Abd Aziz NH. Autologous Human Mesenchymal Stem Cell-Based Therapy in Infertility: New Strategies and Future Perspectives. Biology (Basel). 2023;12(1):108. doi: 10.3390/biology12010108.
20. Wang Y, Yin LL, Sun XF, Yang Q, Yu YQ, Rong YX, et al. Retrospective analysis of autologous bone marrow mesenchymal stem cells as adjuvant therapy in recurrent intrauterine adhesions. Arch Gynecol Obstet. 2025. doi: 10.1007/s00404-025-07952-5.
21. Zhang WY, Wang HB, Deng CY. Advances in human umbilical cord mesenchymal stem cells-derived extracellular vesicles and biomaterial assemblies for endometrial injury treatment. World J Stem Cells. 2025;17(1):97905. doi: 10.4252/wjsc.v17.i1.97905.
22. Rajabloo Y, Al-Asady AM, Avan A, Khazaei M, Ryzhikov M, Hassanian SM. Unlocking Therapeutic Potential: Mesenchymal Stem Cells-derived Exosomes in IUA Treatment, Current Status and Perspectives. Curr Pharm Des. 2025. doi: 10.2174/0113816128337236241210080728.
23. Busari KA, Tulay P. Polycystic ovary syndrome: emerging stem cell therapies. Rev Assoc Med Bras (1992). 2024;70(6):e20231436. doi: 10.1590/1806-9282.20231436.
24. Park H, Han JW, Kim GJ. Recent trends in polycystic ovary syndrome treatment based on adult stem cell therapies. Clin Exp Reprod Med. 2025. doi: 10.5653/cerm.2024.07248.
25. Hu L, Tan R, He Y, Wang H, Pu D, Wu J. Stem cell therapy for premature ovarian insufficiency: a systematic review and meta-analysis of animal and clinical studies. Arch Gynecol Obstet. 2023. doi: 10.1007/s00404-023-07062-0.
26. Iskakov Y, Omarbayev R, Nugumanov R, Turgunbayev T, Yermaganbetov Y. Treatment of erectile dysfunction by intracavernosal administration of mesenchymal stem cells in patients with diabetes mellitus. Int Braz J Urol. 2024;50. doi: 10.1590/S1677-5538.IBJU.2024.0100.
27. Daneshwar D, Lee Y, Nordin A. Stem cell assisted low-intensity shockwave for erectile dysfunction treatment: Current perspective. Regen Ther. 2024;26:1150-1158. doi: 10.1016/j.reth.2024.11.006.
28. Zhang X, Yang M, Chen X, Lu M. Research progress on the therapeutic application of extracellular vesicles in erectile dysfunction. Sex Med Rev. 2024:qeae022. doi: 10.1093/sxmrev/qeae022.
29. Chakra MA, Bailly H, Klampke F, Boaz J, Jida M, Yassine AA, et al. An update on the use of stem cell therapy for erectile dysfunction. Asian J Urol. 2024;11(4):530-544. doi: 10.1016/j.ajur.2023.07.005.
30. Sonawane T, Kashte S, Khera S, Bahulkar A, Cuddapah C, Kadam S. Interrogating erectile dysfunction and evaluating novel therapeutic frontiers, with emphasis on stem cell strategies. J Assist Reprod Genet. 2024. doi: 10.1007/s10815-024-03165-y.
31. Hinojosa-Gonzalez DE, Saffati G, Orozco Rendon D, La T, Kronstedt S, Muthigi A, Khera M. Regenerative therapies for erectile dysfunction: a systematic review, Bayesian network meta-analysis, and meta-regression. J Sex Med. 2024:qdae131. doi: 10.1093/jsxmed/qdae131.
32. Patel AA, Shafie A, Mohamed AH, Ali SA, Tayeb FJ, Waggiallah HA, et al. The promise of mesenchymal stromal/stem cells in erectile dysfunction treatment: a review of current insights and future directions. Stem Cell Res Ther. 2025;16(1):98. doi: 10.1186/s13287-025-04221-9.

AGING AND FRAILTY

The remarkable advances in biology and medicine have succeeded in extending life expectancy, leading to a demographic transition marked by an increasing elderly population across all countries. However, the prevalence of age-related diseases has also increased, reflecting a progressive decline in the body's ability to maintain biological balance with advancing age and resulting in a greater incidence of chronic, debilitating, and painful conditions (1). Accordingly, there is a growing need to elucidate the mechanisms underlying aging and to develop novel therapeutic strategies aimed, at the very least, at making the process more manageable. For this reason, the World Health Organization is committed to promoting measures that ensure what it refers to as "healthy aging," which it defines as "the process of developing and maintaining the functional ability that enables well-being in older age." Functional ability is about "having the capabilities that enable all people to be and do what they have reason to value" (https://www.who.int/news-room/questions-and-answers/item/healthy-ageing-and-functional-ability).

Although chronological age correlates with several clinical conditions, it does not always accurately reflect an individual's functional capacity, overall well-being, or risk of mortality. In contrast, biological age provides better information about an individual's health status and indicates how rapidly or slowly they are aging. Technological advances have facilitated the identification of aging biomarkers, and the "biological clocks" are algorithms built from these markers, allowing for the estimation of an individual's biological age (2). More than a dozen aging biomarkers have been identified, including genomic instability, telomere shortening, epigenetic alterations, mitochondrial dysfunction, chronic inflammation with excessive production of free radicals, stem cell senescence, and microbiota imbalances, among others. These biomarkers are intricately interconnected, and many of them represent potential targets for anti-aging therapy (1,3-5).

The *frailty syndrome* in older adults is characterized by reduced muscle mass, tone, and strength; slowed mobility and decreased physical activity; weight loss; fatigability; a decline in physiological functions; and elevated levels of molecular markers of inflammation. It constitutes a major predisposing factor for falls, disability, and hospitalization among the elderly. Although timely healthcare interventions such as exercise, proper nutrition, social engagement, and pharmacological treatments can improve quality of life and reduce healthcare costs, no specific treatment currently exists for managing frailty in older adults. Given that stem cells and exosomes possess biological properties that may help control or even reverse many of the signs and symptoms of frailty, regenerative medicine has generated significant interest as a therapeutic option, especially considering that, as stem cells become senescent, they begin to secrete degenerative factors that negatively affect young stem cells and progressively lose their therapeutic potential.

The regenerative capacity of stem cells/exosomes, as well as their ability to modulate chronic inflammation, reduce biochemical markers of senescence, restore mitochondrial function (the cellular energy centers), and regulate immunosenescence (the aging of the immune system) and the loss of muscle tone and mass (sarcopenia), has been well documented in the scientific literature. Moreover, they have shown benefits in other clinical conditions frequently associated with frailty, such as chronic lung disease, cardiovascular disease, diabetes, osteoarthritis, and osteoporosis, among others (2,6-20).

REFERENCES

1. Nunkoo VS, Cristian A, Jurcau A, Diaconu RG, Jurcau MC. The Quest for Eternal Youth: Hallmarks of Aging and Rejuvenating Therapeutic Strategies. Biomedicines. 2024;12(11):2540. doi: 10.3390/biomedicines12112540.

2. Lyu YX, Fu Q, Wilczok D, Ying K, King A, Antebi A, et al. Longevity biotechnology: bridging AI, biomarkers, geroscience and clinical applications for healthy longevity. Aging (Albany NY). 2024;16. doi: 10.18632/aging.206135.

3. Roato I, Visca M, Mussano F. Suppressing the Aging Phenotype of Mesenchymal Stromal Cells: Are We Ready for Clinical Translation? Biomedicines. 2024;12(12):2811. doi: 10.3390/biomedicines12122811.

4. Rasouli M, Naeimzadeh Y, Hashemi N, Hosseinzadeh S. Age-Related Alterations in Mesenchymal Stem Cell Function: Understanding Mechanisms and Seeking Opportunities to Bypass the Cellular Aging. Curr Stem Cell Res Ther. 2023. doi: 10.2174/1574888X18666230113144016.

5. Conde L, Lucas C. The Benjamin Button effect on stem cells: Reversing the clock on aging immunity. Sci Immunol. 2024;9(95):eadq0013. doi: 10.1126/sciimmunol.adq0013.

6. Branco A, Moniz I, Ramalho-Santos J. Mitochondria as biological targets for stem cell and organismal senescence. Eur J Cell Biol. 2023;102(2):151289. doi: 10.1016/j.ejcb.2023.151289.

7. Tian X, Pan M, Zhou M, Tang Q, Chen M, Hong W, et al. Mitochondria Transplantation from Stem Cell for Mitigating Sarcopenia. Aging Dis. 2023. doi: 10.14336/AD.2023.0210.

8. Li N, Liu G, Gao H, Wu Q, Meng J, Wang F, Jiang S, Chen M, Xu W, Zhang Y, Wang Y, Feng Y, Liu J, Xu C, Lu H. Geriatric syndromes, chronic inflammation, and advances in the management of frailty: A review with new insights. Biosci Trends. 2023. doi: 10.5582/bst.2023.01184.

9. Yuan HL, Chang L, Fan WW, Liu X, Li Q, Tian C, et al. Application and challenges of stem cells in cardiovascular aging. Regen Ther. 2023;25:1-9. doi: 10.1016/j.reth.2023.11.009.

10. El Assaad N, Chebly A, Salame R, Achkar R, Bou Atme N, Akouch K, et al. Anti-aging based on stem cell therapy: A scoping review. World J Exp Med. 2024;14(3):97233. doi: 10.5493/wjem.v14.i3.97233.

11. Nunes-Pinto M, Bandeira de Mello RG, Pinto MN, Moro C, Vellas B, Martinez LO, et al. Sarcopenia and the biological determinants of aging: A narrative review from a geroscience perspective. Ageing Res Rev. 2024:102587. doi: 10.1016/j.arr.2024.102587.

12. Rudnitsky E, Braiman A, Wolfson M, Muradian KK, Gorbunova V, Turgeman G, Fraifeld VE. Stem cell-derived extracellular vesicles as senotherapeutics. Ageing Res Rev. 2024:102391. doi: 10.1016/j.arr.2024.102391.

13. Chang L, Fan WW, Yuan HL, Liu X, Wang Q, Ruan GP, et al. Role of umbilical cord mesenchymal stromal cells in skin rejuvenation. NPJ Regen Med. 2024;9(1):20. doi: 10.1038/s41536-024-00363-1.

14. Zhu Y, Huang C, Zheng L, Li Q, Ge J, Geng S, et al. Safety and efficacy of umbilical cord tissue-derived mesenchymal stem cells in the treatment of patients with aging frailty: a phase I/II randomized, double-blind, placebo-controlled study. Stem Cell Res Ther. 2024;15(1):122. doi: 10.1186/s13287-024-03707-2.

15. Alibhai FJ, Li RK. Rejuvenation of the Aging Heart: Molecular Determinants and Applications. Can J Cardiol. 2024:S0828-282X(24)00201-0. doi: 10.1016/j.cjca.2024.03.004.

16. Zhang A, Li Q, Chen Z. Therapeutic Efficacy and Promise of Human Umbilical Cord Mesenchymal Stem Cell-Derived Extracellular Vesicles in Aging and Age-Related Disorders. Int J Mol Sci. 2024;26(1):225. doi: 10.3390/ijms26010225.

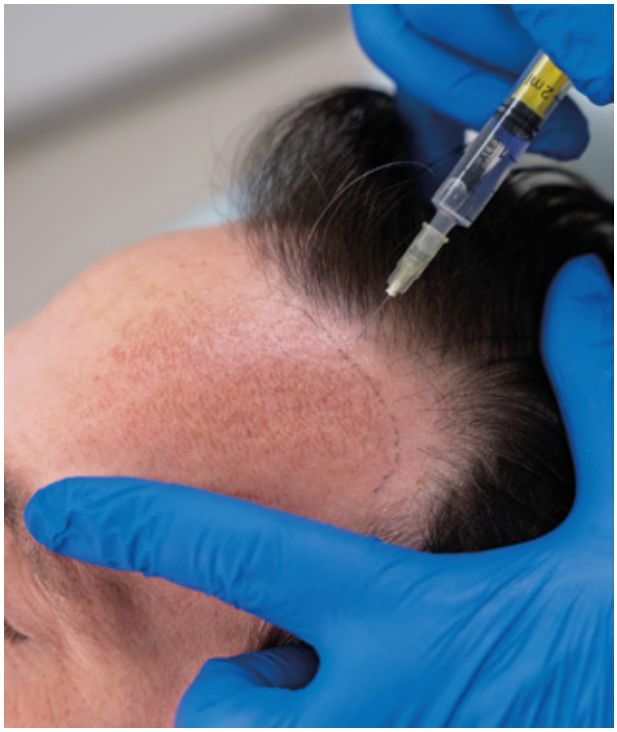
17. Wei B, Wei M, Huang H, Fan T, Zhang Z, Song X. Mesenchymal Stem Cell-Derived Exosomes: A Promising Therapeutic Strategy for Age-Related Diseases. Cell Prolif. 2024:e13795. doi: 10.1111/cpr.13795.

18. Quan J, Liu Q, Li P, Yang Z, Zhang Y, Zhao F, et al. Mesenchymal stem cell exosome therapy: current research status in the treatment of neurodegenerative diseases and the possibility of reversing normal brain aging. Stem Cell Res Ther. 2025;16(1):76. doi: 10.1186/s13287-025-04160-5.

19. Xiao N, Li Q, Liang G, Qian Z, Lin Y, Zhang H, et al. Regulatory Roles of Exosomes in Aging and Aging-Related Diseases. Biogerontology. 2025;26(2):61. doi: 10.1007/s10522-025-10200-7.

20. Rogina B, Anderson R, Lebrasseur N, Curan S, Yousefzadeh MJ, Ghosh B, et al. Symposia Report of The Annual Biological Sciences Section Meeting of the Gerontological Society of America 2023, Tampa, Florida. J Gerontol A Biol Sci Med Sci. 2025:glaf026. doi: 10.1093/gerona/glaf026.

SKIN DISORDERS AND ALOPECIA AESTHETIC MEDICINE



SKIN LESIONS

The benefits of stem cells/exosomes, and growth factors have been extensively studied and confirmed not only in aesthetic medicine but also across a wide range of skin diseases and lesions caused by chronic inflammation, infections, trauma, burns, surgeries, aesthetic procedures, neuropathies, and vascular insufficiency, with varying outcomes (1-4).

Several reviews and meta-analyses of clinical trials investigating the effects of stem cells/exosomes in the treatment of ulcers and chronic skin wounds confirm that regenerative therapy is a safe procedure associated with significant improvement in conditions such as venous ulcers, diabetic foot ulcers, and ulcers secondary to severe ischemic disease, leading to a reduction in amputation rates. The intralesional application of stem cells/exosomes for the treatment of scars is a simple, safe, and effective approach, not only in clinical but also in histological terms. The prophylactic intradermal application of stem cells in surgical wounds helps prevent the formation of postoperative hypertrophic scars while preserving the normal structure and function of the skin. For these reasons, many experts consider stem cell/exosome based regenerative therapy a novel and effective treatment alternative, particularly when combined with appropriate medical and surgical interventions (5-9).

ALOPECIA

Thanks to the regenerative properties of stem cells and their ability to release factors that stimulate hair growth, hair regeneration has become a key focus of regenerative medicine. Several studies have reported beneficial outcomes with minimal adverse effects, positioning stem cell therapy as one of the most promising and potentially effective treatments for various forms of alopecia (10–15).

AESTHETIC MEDICINE

The skin is a tissue with a high capacity for renewal, but it is continuously exposed to adverse environmental conditions, such as ultraviolet radiation, which causes structural damage and loss of vitality. As a result, skin aging is inevitable, although it can be slowed down. Regenerative medicine has emerged as a novel strategy for facial rejuvenation, the filling of furrows and expression lines, and the treatment of scars, acne, vitiligo lesions, and other skin conditions (10,14-25).

REFERENCES

1. Jafarzadeh A, Pour Mohammad A, Keramati H, Zeinali R, Khosravi M, Goodarzi A. Regenerative medicine in the treatment of specific dermatologic disorders: a systematic review of randomized controlled clinical trials. Stem Cell Res Ther. 2024;15(1):176. doi: 10.1186/s13287-024-03800-6.

2. Park SY, Yi KH. Exosome-mediated Advancements in Plastic Surgery: Navigating Therapeutic Potential in Skin Rejuvenation and Wound Healing. Plast Reconstr Surg Glob Open. 2024;12(8):e6021. doi: 10.1097/GOX.0000000000006021.

3. Dukharan V, Shah M, Broughton L, Stegura C, Samman L, Schur N, Schlesinger T. The Role of Exosomes in Medical Dermatology: Literature Review and Update. J Cosmet Dermatol. 2025;24(1):e16761. doi: 10.1111/jocd.16761.

4. Razavi ZS, Aliniay Sharafshadehi S, Yousefi MH, Javaheri F, Rahimi Barghani MR, Afkhami H, Heidari F. Application of novel strategies in chronic wound management with focusing on pressure ulcers: new perspective. Arch Dermatol Res. 2025;317(1):320. doi: 10.1007/s00403-024-03790-8.

5. Mrozikiewicz-Rakowska B, Szabłowska-Gadomska I, Cysewski D, Rudziński S, Płoski R, Gasperowicz P, et al. Allogenic Adipose-Derived Stem Cells in Diabetic Foot Ulcer Treatment: Clinical Effectiveness, Safety, Survival in the Wound Site, and Proteomic Impact. Int J Mol Sci. 2023;24(2):1472. doi: 10.3390/ijms24021472.

6. Wu S, Zhou Z, Li Y, Jiang J. Advancements in diabetic foot ulcer research: Focus on mesenchymal stem cells and their exosomes. Heliyon. 2024;10(17):e37031. doi: 10.1016/j.heliyon.2024.e37031.

7. Huerta CT, Voza FA, Ortiz YY, Liu ZJ, Velazquez OC. Mesenchymal stem cell-based therapy for non-healing wounds due to chronic limb-threatening ischemia: A review of preclinical and clinical studies. Front Cardiovasc Med. 2023. doi: 10.3389/fcvm.2023.1113982.

8. Camesi A, Wettstein R, Valido E, Nyfeler N, Stojic S, Glisic M, et al. Advancements in cell-based therapies for the treatment of pressure injuries: A systematic review of interventional studies. J Tissue Eng. 2024;14:20417314231201071. doi: 10.1177/20417314231201071.

9. Li R, Wang H, Wang X, Yang Y, Zhong K, Zhang X, Li H. MSC-EVs and UCB-EVs promote skin wound healing and spatial transcriptome analysis. Sci Rep. 2025;15(1):4006. doi: 10.1038/s41598-025-87592-6.

10. Norouzi F, Aghajani S, Vosoughi N, Sharif S, Ghahremanzadeh K, Mokhtari Z, Verdi J. Exosomes derived stem cells as a modern therapeutic approach for skin rejuvenation and hair regrowth. Regen Ther. 2024;26:1124-1137. doi: 10.1016/j.reth.2024.10.001.

11. Gasteratos K, Kouzounis K, Goverman J. Autologous Stem Cell-derived Therapies for Androgenetic Alopecia: A Systematic Review of Randomized Control Trials on Efficacy, Safety, and Outcomes. Plast Reconstr Surg Glob Open. 2024;12(2):e5606. doi: 10.1097/GOX.0000000000005606.

12. Ersan M, Ozer E, Akin O, Tasli PN, Sahin F. Effectiveness of Exosome Treatment in Androgenetic Alopecia: Outcomes of a Prospective Study. Aesthetic Plast Surg. 2024. doi: 10.1007/s00266-024-04332-3.

13. Pozo-Pérez L, Tornero-Esteban P, López-Bran E. Clinical and preclinical approach in AGA treatment: a review of current and new therapies in the regenerative field. Stem Cell Res Ther. 2024;15(1):260. doi: 10.1186/s13287-024-03801-5.

14. Karimi N, Dinçsoy AB. The Role of Mesenchymal Stem Cell-Derived Exosomes in Skin Regeneration, Tissue Repair, and the Regulation of Hair Follicle Growth. Adv Exp Med Biol. 2025. doi: 10.1007/5584_2024_839.

15. Shah M, Dukharan V, Broughton L, Stegura C, Schur N, Samman L, Schlesinger T. Exosomes for Aesthetic Dermatology: A Comprehensive Literature Review and Update. J Cosmet Dermatol. 2025;24(1):e16766. doi: 10.1111/jocd.16766.

16. Park GH, Kwon HH, Seok J, Yang SH, Lee J, Park BC, et al. Efficacy of combined treatment with human adipose tissue stem cell-derived exosome-containing solution and microneedling for facial skin aging: A 12-week prospective, randomized, split-face study. J Cosmet Dermatol. 2023. doi: 10.1111/jocd.15872.

17. Cai CS, He GJ, Xu FW. Advances in the Applications of Extracellular Vesicle for the Treatment of Skin Photoaging: A Comprehensive Review. Int J Nanomedicine. 2023;18:6411-6423. doi: 10.2147/IJN.S433611.

18. Alquraisy A, Wilar G, Mohammed AFA, El-Rayyes A, Suhandi C, Wathoni N. A Comprehensive Review of Stem Cell Conditioned Media Role for Anti-Aging on Skin. Stem Cells Cloning. 2024;17:5-19. doi: 10.2147/SCCAA.S480437.

19. Gui Q, Ding N, Yao Z, Wu M, Fu R, Wang Y, et al. Extracellular vesicles derived from mesenchymal stem cells: the wine in Hebe's hands to treat skin aging. Precis Clin Med. 2024;7(1):pbae004. doi: 10.1093/pcmedi/pbae004.

20. Putri WE, Widyaswari MS, Prakoeswa CRS, Muhammad DS, Romadhani DF, Nisaussholihah N. The Effect of Human Adipose Stem Cell-Conditioned Medium (hASC-CM) in Photoaged Skin. J Stem Cells Regen Med. 2024;20(2):47-52. doi: 10.46582/jsrm.2002006.

21. Almadori A, Butler PE. Scarring and Skin Fibrosis Reversal with Regenerative Surgery and Stem Cell Therapy. Cells. 2024;13(5):443. doi: 10.3390/cells13050443.

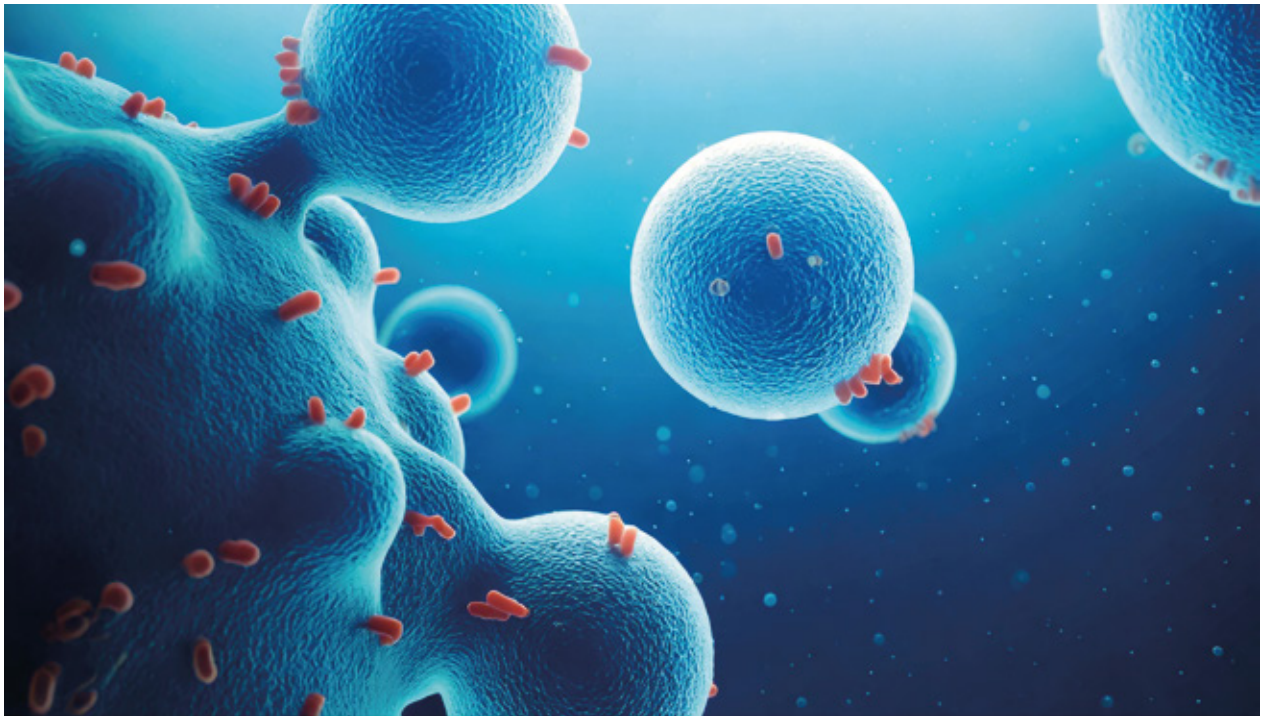
22. Yu H, Zhang B, Zhan Y, Yi Y, Jiang Q, Zhang Q, et al. Neutrophil extracellular trap-related mechanisms in acne vulgaris inspire a novel treatment strategy with adipose-derived stem cells. Sci Rep. 2024;14(1):1521. doi: 10.1038/s41598-024-51931-w.

23. Cheng L, Liu J, Wang Q, Hu H, Zhou L. The Protective Effect of a Human Umbilical Cord Mesenchymal Stem Cell Supernatant on UVB-Induced Skin Photodamage. Cells. 2024;13(2):156. doi: 10.3390/cells13020156.

24. Bicer M. Revolutionizing dermatology: harnessing mesenchymal stem/stromal cells and exosomes in 3D platform for skin regeneration. Arch Dermatol Res. 2024;316(6):242. doi: 10.1007/s00403-024-03055-4.

25. Jung H, Jung Y, Seo J, Bae Y, Kim HS, Jeong W. Roles of extracellular vesicles from mesenchymal stem cells in regeneration. Mol Cells. 2024:100151. doi: 10.1016/j.mocell.2024.100151.

EXTRACELLULAR VESICLES (EVs)

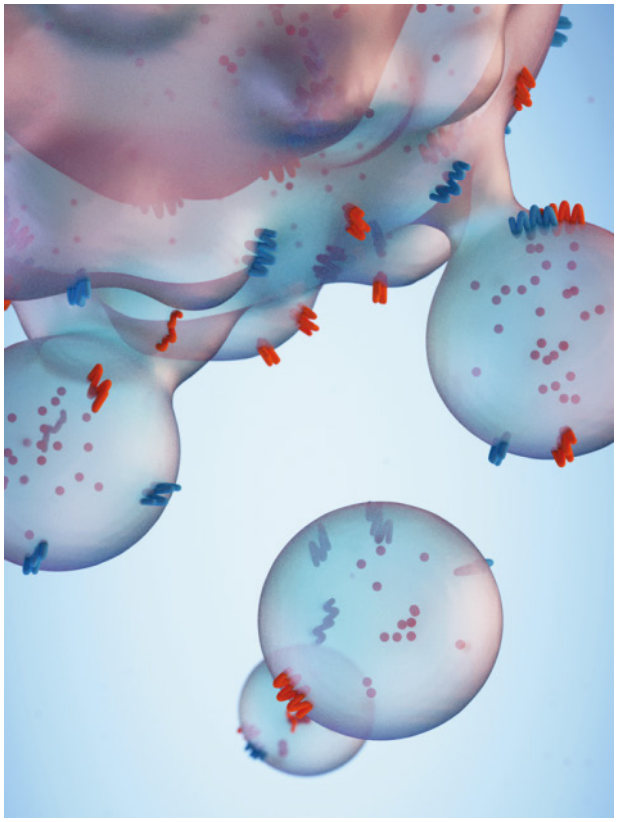


All cells have the ability to secrete biologically active molecules into their surrounding environment, contributing to tissue repair and maintaining their vitality or that of other organs (paracrine activity). One mechanism by which cells optimize this function is through the release of hundreds of active molecules, packaged in membrane-bound vesicles that resemble the cell membrane. Proteins, lipids, nucleic acids, and other biologically active factors are transported within these vesicles, which can be transferred to recipient cells to modify their functional state. These vesicles play a pivotal role in the paracrine activity of cells and cell-to-cell communication (1).

These vesicles are classified based on their size and the cellular compartment from which they originate. *Exosomes*are vesicles ranging from 30 to 120 nm in diameter; *microvesicles*(or ectosomes) range from 50 nm to 1 µm, while *apoptotic bodies* measure between 50 nm and 2 µm. In addition to their size, they also differ in the composition of their biologically active molecules. It should be noted, however, that current techniques for isolating the different types of vesicles are not yet sufficiently refined, making the classification into these three categories imprecise. Therefore, the use of the more general term “extracellular vesicles” (EVs) has been proposed. Nevertheless, the term “exosomes” remains more commonly used in the literature (1,2).

Although EVs are released by all cell types, in this section we focus exclusively on those derived from stem cells, as they exhibit biological properties similar to the cells from which they originate. In other words, they retain the ability to replicate nearly all the therapeutic activities demonstrated by stem cells, suggesting that they may be used for the same therapeutic indications as their cells of origin (3).

Additionally, EVs possess several advantages over the cells from which they are derived. Due to their small size and the physicochemical properties of their membranes, EVs can cross all types of biological barriers, distribute easily throughout the body, and penetrate deeply into tissues. Their small size and lack of immunogenicity also allow them to evade destruction by the patient's immune system. Unlike living cells, EVs are non-replicating and do not carry the risk of tumor formation, thereby avoiding many of the ethical and legal concerns associated with the use of live cells. Furthermore, they can be easily modified, are stable, and can be stored for extended periods (4,5).



Beyond their therapeutic attributes, the medical potential of EVs extends further: they can be used to transport and deliver drugs to tissues that would otherwise be inaccessible to the target organ, or conversely, to prevent distribution to organs where they could cause harm. As drug delivery systems, EVs are less immunogenic and more biocompatible than the synthetic particles conventionally used by the pharmaceutical industry for systemic drug transport (6). Finally, since all cells are capable of producing EVs, they have potential as biomarkers for the early diagnosis of various diseases, including cancer and neurodegenerative disorders (7,8).

Although the use of EVs as therapeutic tools is highly promising, this strategy still faces several challenges and limitations, including the availability of an adequate stem cell source; difficulties in identification, isolation, and purification; storage conditions that preserve biological activity; the determination of optimal doses and administration routes; and confirmation of long-term safety and efficacy.

REFERENCES

1. Rai A, Claridge B, Lozano J, Greening DW. The Discovery of Extracellular Vesicles and Their Emergence as a Next-Generation Therapy. Circ Res. 2024;135(1):198-221. doi: 10.1161/CIRCRESAHA.123.323054

2. Li Z, Yan J, Li X, Chen H, Lin C, Zhang Y, Gao T, Zhang Y, Shu Y, Pan S, Zhang Y. Advancements in extracellular vesicles biomanufacturing: a comprehensive overview of large-scale production and clinical research. Front Bioeng Biotechnol. 2025;13:1487627. doi: 10.3389/fbioe.2025.1487627.

3. Tan F, Li X, Wang Z, Li J, Shahzad K, Zheng J. Clinical applications of stem cell-derived exosomes. Signal Transduct Target Ther. 2024;9(1):17. doi: 10.1038/s41392-023-01704-0.

4. Karimian A, Khoshnazar SM, Kazemi T, Asadi A, Abdolmaleki A. Role of secretomes in cell-free therapeutic strategies in regenerative medicine. Cell Tissue Bank. 2023. doi: 10.1007/s10561-023-10073-5.

5. Abdulmalek OAAY, Husain KH, AlKhalifa HKAA, Alturani MMAB, Butler AE, Moin ASM. Therapeutic Applications of Stem Cell-Derived Exosomes. Int J Mol Sci. 2024;25(6):3562. doi: 10.3390/ijms25063562.

6. Thakur A, Rai D. Global requirements for manufacturing and validation of clinical grade extracellular vesicles. J Liq Biopsy. 2024;6:100278. doi: 10.1016/j.jlb.2024.100278.

7. Rafanan J, Ghani N, Kazemeini S, Nadeem-Tariq A, Shih R, Vida TA. Modernizing Neuro-Oncology: The Impact of Imaging, Liquid Biopsies, and AI on Diagnosis and Treatment. Int J Mol Sci. 2025;26(3):917. doi: 10.3390/ijms26030917.

8. Rajendran RL, Gangadaran P, Ghosh S, Nagarajan AK, Batabyal R, Ahn BC. Unlocking the secrets of single extracellular vesicles by cutting-edge technologies. Pathol Res Pract. 2025;269:155878. doi: 10.1016/j.prp.2025.155878.

GENERATING

LIFE

Regencord

Cra. 13 Av. 30 de Agosto, 105-31 Belmonte Bajo,
Clínica Central del Eje. Pereira, Colombia.
Tel: +57 (606) 321 0051 / Cel: +57 313 870 3120